THE CHEMISTRY OF NATURAL PRODUCTS
VOLUME I

K. W. BENTLEY

THE ALKALOIDS

CFTRI-MYSORE
10621
Alkaloids: Part-..

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THE CHEMISTRY OF NATURAL PRODUCTS
K. W. BENTLEY, *Editor*

Volume I

THE ALKALOIDS

By K. W. Bentley

THE CHEMISTRY OF NATURAL PRODUCTS
A series of texts on the constitution of natural products
K. W. BENTLEY, *Editor*

VOLUME I

THE ALKALOIDS

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PART I

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Alkaloids: Part-...

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PREFACE

There appears at present to be no source of information available to the undergraduate student on the large and expanding field of Organic Chemistry dealing with Natural Products intermediate between the general text books (in which treatment of the subject is necessarily very limited) and the comprehensive monographs (from which it is usually very difficult for the average student to extract the vital information, and which are in any case frequently beyond the means of most students). The aim of this book, and of the series of which this is the first, is to fill this gap at, it is hoped, a reasonable price, and to present to the reader an account, shorn of all frills and unnecessary discussion, of the salient features of the degradative and synthetic work on which the structures of representatives of the major groups of natural products are based.

The present volume is devoted to a consideration of the ten most important groups of alkaloids; other groups have necessarily been omitted in order to limit the work to a reasonable size and cost, but it is hoped that the groups discussed will prove sufficiently representative of the naturally occurring bases for the students needs.

Verbal discussion has been reduced to the minimum consistent with clarity and in many cases self-explanatory formulas have been allowed to speak for themselves. It is hoped that the relatively large number of formulas used in the text will make for easier understanding of the subject. Two important abbreviations are used in the formulas, namely: HD, which represents *Hofmann degradation* (one stage), i.e., the degradation of quaternary hydroxides by dry distillation or by heating with aqueous or alcoholic alkali, and EM, which represents *exhaustive methylation*, i.e., as many stages of Hofmann degradation as are necessary for the complete removal of a nitrogen atom from a compound.

I wish to acknowledge my debt to the series of volumes entitled *The Alkaloids*, edited by R. H. F. Manske and H. L. Holmes, published by Academic Press, Inc., New York, which has proved an invaluable lead to important references. Frequent reference is made to this work in the text as a source of further and more detailed accounts of the groups of alkaloids considered, and, as it is now a standard work of reference, to save space it is referred to simply as *The Alkaloids.*

My thanks are due to Messrs. J. C. Ball, J. P. Ringe, and S. F. Dyke for their assistance in the checking of the proofs and to my wife for her help in the compilation of the index and for general encouragement.

Aberdeen, Scotland K. W. B.
April 1957

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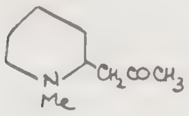
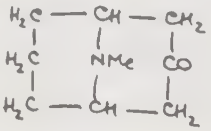
INTRODUCTION

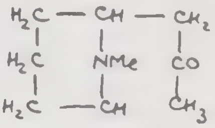
The term *Alkaloid* is applied to the members of a class of natural products of a basic nature, and is derived from the name "vegetable alkali" first applied to these substances. They all owe their basic nature to an amino nitrogen. They occur in the leaves, seeds, roots, and bark of plants, particularly of the families Papaveraceae (poppies), Papilonaceae (lupins), Ranunculae (aconites), and Solanaceae (tobacco, potato), from which they may be extracted by ethanol or, after making alkaline, by ether or ethyl acetate. The separation of mixtures of alkaloids so obtained can be a very tedious task, but may be accomplished by fractional crystallization, fractional precipitation, partition chromatography on columns, or by countercurrent extraction.

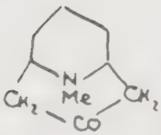
Alkaloids as a class have interested organic chemists partly on account of their physiological action on the animal organism, and partly on account of the complex structural and synthetical puzzles that they pose. The chemistry of the alkaloids is but a branch of the wide chemistry of nitrogenous heterocyclic compounds, but the methods by which the structures of individual bases are deduced from degradative evidence and confirmed by total synthesis are typical of the methods applied for these purposes in the whole field of the chemistry of natural products and illustrative of the general fundamental principles of organic chemistry.

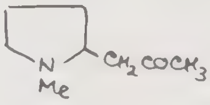
No systematic nomenclature or structural classification for alkaloids exists but an attempt has been made to arrange the following chapters, and the material in each chapter, in some sort of order by beginning with the simplest ring systems and proceeding through those of moderate complexity to those of greater complexity. The representation of the formulas requires some comment. As far as possible the formulas used are drawn in the form customarily found in the literature as this reduces to a minimum the amount of mental gymnastics required if reference is made to other publications. However in doing this the same ring system is, in different places, represented in different ways, and unless attention is drawn to this the relationship between different alkaloids may well be obscured and one of the objects of the book would thus be frustrated. For example, methylisopelletierine is conventionally written as a simple derivative of piperidine as in (I), whereas pseudopelletierine is conventionally written as in (II) and no relationship between the two is immediately obvious on first inspection of the two formulas, but the similarity is revealed clearly if the former is represented by the differently drawn structure (III) or the latter by (IV). In the same way hygrin (V) is closely related to tropinone (VI). Accordingly the ground covered in each chapter, showing the basic ring systems of the group and of the principal members of the subgroups, and the relationship between different conventions used for representation, is outlined in the following pages.

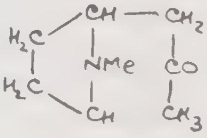

(I)


(II)


(III)


(IV)

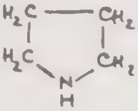

(V)


(VI)

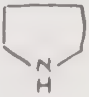
To facilitate the rapid identification of the structure of each alkaloid the number of the appropriate formula is given in bold type after the initial heading for that base, e.g., in Chapter 1, B. Cuscohygrin (XVIII) and C. Cocaine (XCIII). For each alkaloid discussed the degradative evidence leading up to the elucidation of the structure is first presented, followed by an outline of the total synthesis of the base or of one of its derivatives where such a synthesis has been achieved.

Chapter I. The Alkaloids of the Pyrrolidine Group

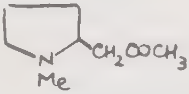
Basic ring system pyrrolidine:



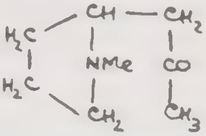
or



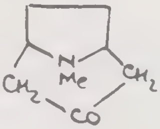
1. The Hygrine Group, e.g., hygrine:



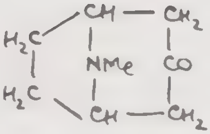
also written:



2. The Tropane Group, e.g., tropinone:

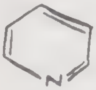


or conventionally

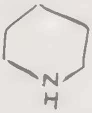


Chapter II. The Alkaloids of the Pyridine—Piperidine Group

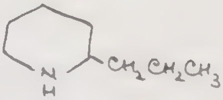
Basic rings systems pyridine:



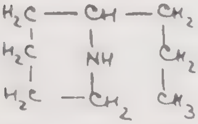
and piperidine:

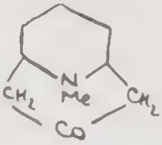


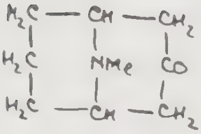
1. Simple Piperidine Derivatives, e.g., coniine:



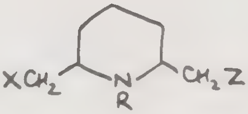
or



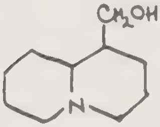
Pseudopelletierine:  conventionally



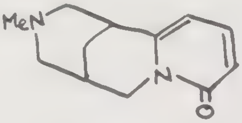
2. The Lobelia Alkaloids of general type:



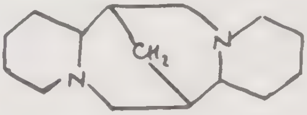
3. The Lupine Alkaloids, divided into three subgroups as shown:



Lupinine

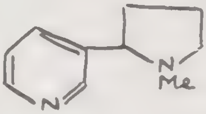


Cytisine

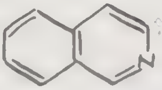


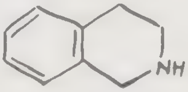
Sparteine

4. The Tobacco Alkaloids, e.g., nicotine:

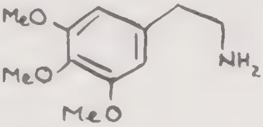


Chapter III. The Alkaloids of the Isoquinoline Group—Part I

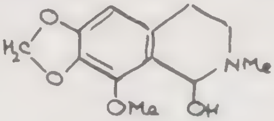
Basic ring systems isoquinoline:  tetrahydroisoquinoline:



1. Uncompleted Isoquinolines and Simple Isoquinolines, e.g.,

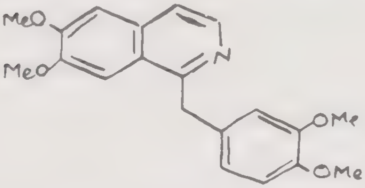


mescaline

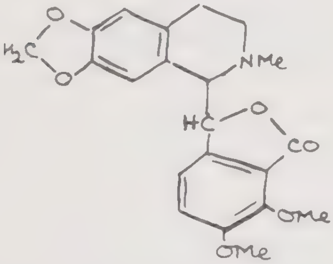


cotarnine

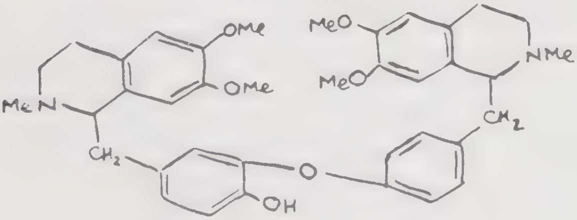
2. Benzylisoquinolines, e.g., papaverine:



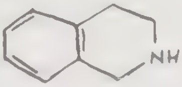
3. Phthalideisoquinolines, e.g., hydrastine:



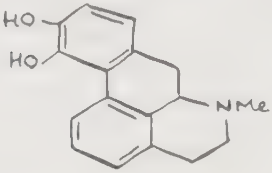
4. Bisbenzylisoquinolines, e.g., dauricine:



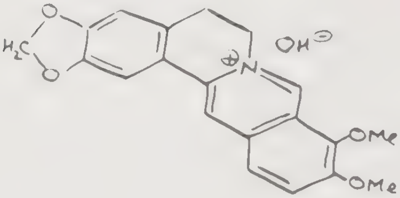
Chapter IV. The Alkaloids of the Isoquinoline Group—Part II

Basic ring system tetrahydroisoquinoline: 

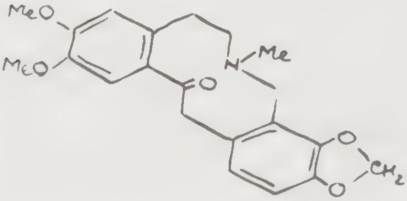
1. The Aporphine Alkaloids, e.g., apomorphine:



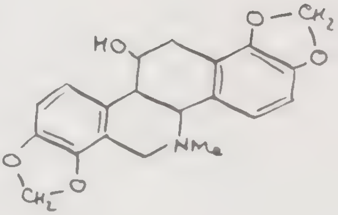
2. The Protoberberine Alkaloids, e.g., berberine:



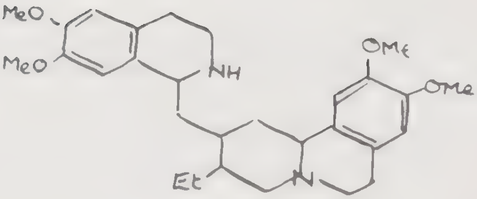
3. The Protopine Alkaloids, e.g., cryptopine:



4. The α-Naphthaphenanthridine
Alkaloids, e.g., chelidonine:

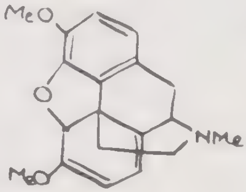


5. Emetine:

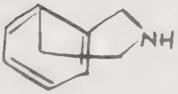


Chapter V. The Alkaloids of the Morphine Group

e.g., thebaine:

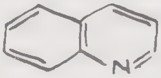


derived from tetrahydroisoquinoline:

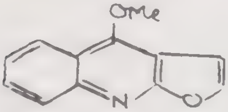


Chapter VI. The Alkaloids of the Quinoline Group

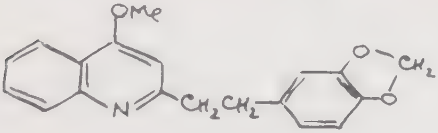
Basic ring system quinoline:



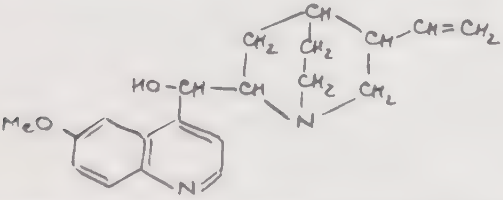
1. The Furoquinoline Alkaloids, e.g., dictamnine:



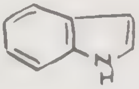
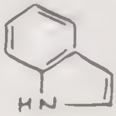
2. The Angostura Alkaloids, e.g., cusparine:



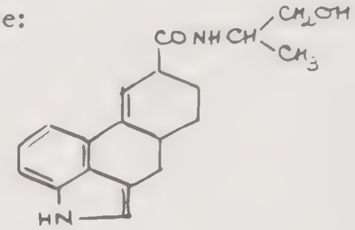
3. The Cinchona Alkaloids, e.g., quinine:



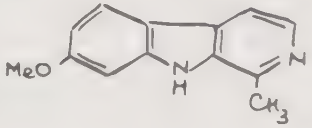
Chapter VII. The Alkaloids of the Indole Group—Part I

Basic ring system indole:  or 

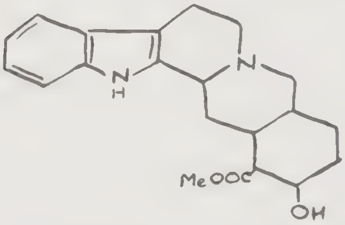
1. The Ergot Alkaloids, e.g., ergonovine:



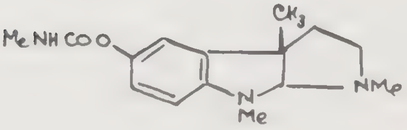
2. The Harmala Alkaloids, e.g., harmine:



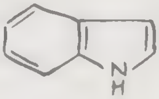
3. Alkaloids of the Yohimbine Group, e.g., yohimbine:



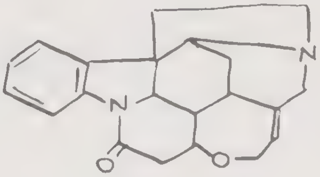
4. Physostigmine:



Chapter VIII. The Alkaloids of the Indole Group—Part II

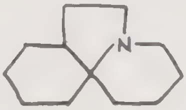
Basic ring system indole: 

Strychnine and brucine, e.g., strychnine:

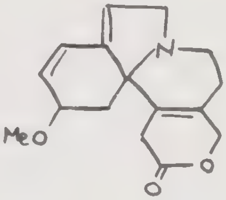


Chapter IX. The Erythrina Alkaloids

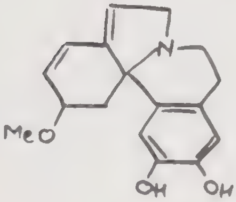
Basic ring system:



β-Erythroidine:

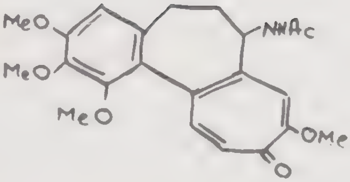


Erysopine:



Chapter X. Colchicine

Colchicine:



CHAPTER 1

ALKALOIDS OF THE PYRROLIDINE GROUP

1. THE HYGRINE GROUP

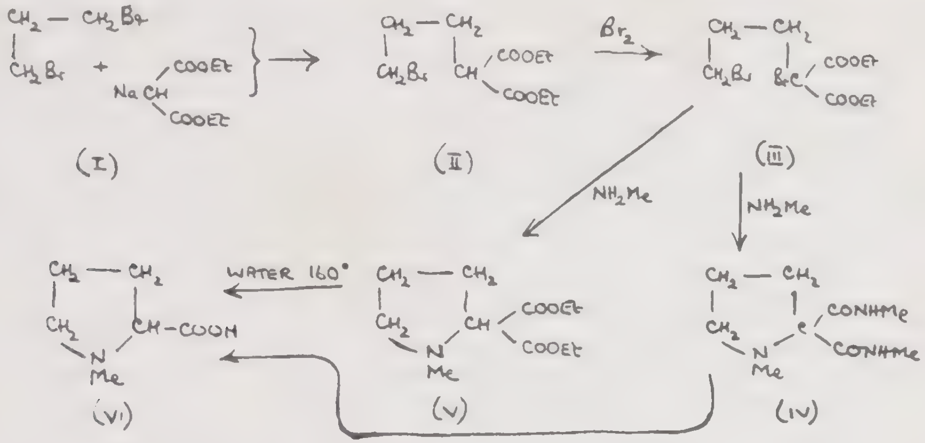
A. Hygrine (X).

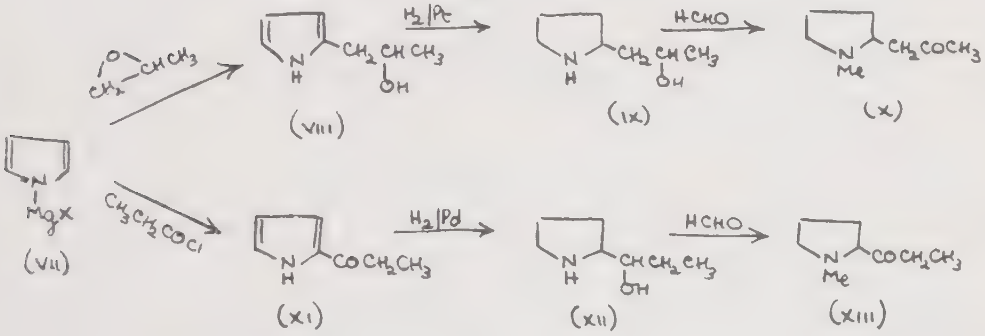
Hygrine, $C_8H_{15}ON$, is the most volatile of the alkaloids of the coca leaf. It contains a carbonyl group and one —NMe— group. On oxidation it affords hygric acid, $C_6H_{11}O_2N$, which on heating yields carbon dioxide and *N*-methylpyrrolidine. The acid was synthesized by Willstätter (34,36) as shown, (I) → (VI). (−)-Hygric acid is obtained by the oxidation of nicotine (12).

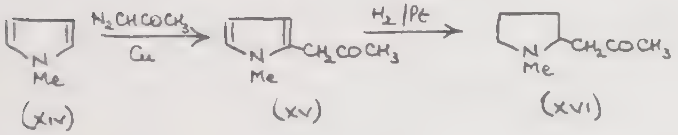
These results lead to two possible structures for hygrine, (X) and (XIII); both these have been synthesized by Hess (7,8) as shown, (VII) → (X) and (VII) → (XIII). In both syntheses the Eschweiler methylation involves simultaneous oxidation of the —CH(OH)— group. The product (X) was shown to be (±)-hygrine. The (±)-alkaloid has also been synthesized by Sorm (24) by the route (XIV) → (XVI). The base hygroline is believed to be the secondary alcohol (XVII) (25).

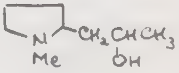
B. Cuscohygrine (XVIII).

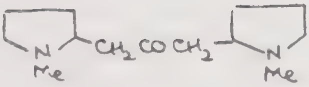
This base is found in "cuscó" leaves and also in *Convolvulus hamadae*. It has the composition $C_{13}H_{24}ON_2$ and is optically inactive. It is ketonic, may be oxidized to hygric acid, and on long standing in ether over potassium hydroxide it is partially converted into (±)-hygrine. The structure (XVIII) was allotted to cuscohygrine by Liebermann (16), but this was modified by Hess (10) to (XIX) on

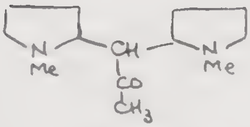







(XVII)


(XVIII)


(XIX)

the grounds that cuscohygrine does not condense with benzaldehyde as it would be expected to do if it contained the system —CH_2—CO—CH_2— and that reduction of the hydrazone gave di-*N*-methylpyrrolidylmethane (XX), though this was subsequently disproved (9).

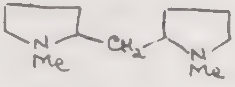
Oxidation of the alkaloid with nitric oxide affords homohygric acid (XXI) (27), subsequently synthesized (13,23). Cuscohygrine itself cannot be exhaustively methylated, but exhaustive methylation of the two stereoisomeric alcohols obtained by reduction of the alkaloid gives *n*-undecane and *n*-undecan-6-ol as final products, if reduction is carried out at each stage. Thus cuscohygrine must contain an unbranched chain of eleven carbon atoms and must be represented by the structure (XVIII) (26). The base has been synthesized in two ways, (XXII) → (XXVI) (20,26) and (XXVII) → (XXVI) (1). The second of these syntheses is based on the Robinson tropinone synthesis (see following section under atropine) and is probably similar to the way in which the alkaloid is formed in the plant (see Chapter 11).

2. THE TROPANE GROUP

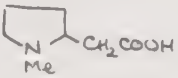
A. Atropine and Hyoscyamine (XLVIII).

(–)-Hyoscyamine, the most common of the alkaloids of the tropane group, was isolated by Geiger and Hesse (5) from henbane. Atropine is the racemic form of the alkaloid, and, though it occurs naturally, it is normally prepared by the racemization of (–)-hyoscyamine by heat or alkali (28). These alkaloids have the composition $C_{17}H_{23}O_3N$ and are easily recognized as esters; on hydrolysis they afford an alcohol, tropine, $C_8H_{15}ON$, and (±)-tropic acid, $C_9H_{10}O_3$. Careful hydrolysis of (–)-hyoscyamine with cold water gives tropine and (–)-tropic acid (4). Evaporation of a solution of tropine tropate results in the formation of a certain amount of atropine.

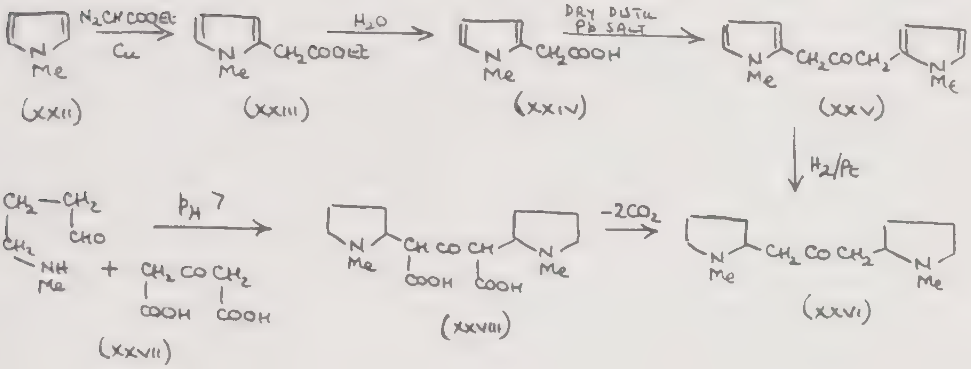
Tropic acid can be dehydrated to atropic acid, which gives phenylglyoxylic acid (XXXII) on oxidation with permanganate. Tropic acid could thus be either (XXIX) or (XXX) and atropic acid (XXXI). That tropic acid is in fact (XXIX) is demonstrated by the synthesis (XXXIII) → (XXXVI) → (XXIX) (19,38). The alternative synthesis (XXXVII) → (XLI) is recommended by MacKenzie and Wood (17).



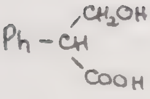
(XX)



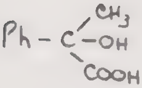
(XXI)



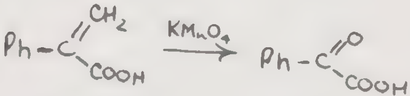
(XXII) (XXIII) (XXIV) (XXV) (XXVI) (XXVII) (XXVIII)



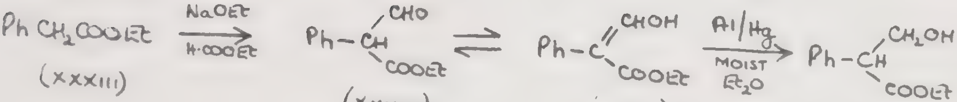
(XXIX)



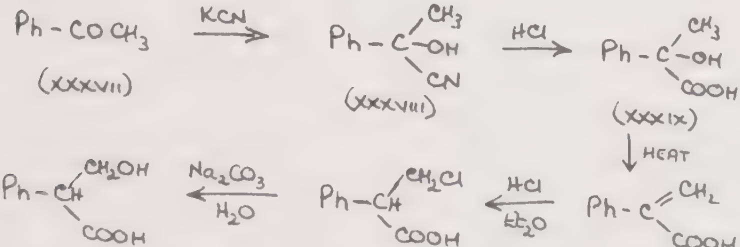
(XXX)



(XXXI) (XXXII)



(XXXIII) (XXXIV) (XXXV) (XXXVI)

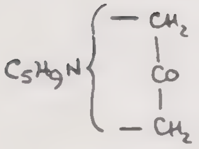


(XXXVII) (XXXVIII) (XXXIX) (XL) (XLI) (XLII)

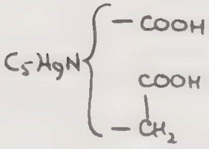
(±)-Tropic acid can be resolved and the separate enantiomorphs can be converted into (+) and (–)-hyoscyamine.

Tropine, $C_8H_{15}ON$, is a strongly basic alcohol the solutions of which absorb carbon dioxide from the air. It can be oxidized by chromic acid to a ketone, tropinone, and is therefore a secondary alcohol (29). Tropinone can be reduced to tropine by zinc and hydrochloric acid and to ψ-tropine, a stereoisomer of tropine, by sodium amalgam. Oxidation of tropine with permanganate affords a secondary base tropigenine (nortropine), $C_7H_{13}ON$ (30), which can be further oxidized by chromic acid to nortropinone (31). The change tropine → nortropine involves only the —NMe— group, which is converted into —NH— + H • CHO. The presence of the —NMe— group in tropine is confirmed by the method of Herzig and Meyer (6).

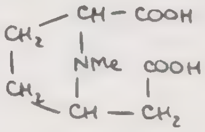
Tropinone can be condensed with benzaldehyde to give a dibenzylidene derivative, and so must contain the system $—CH_2—CO—CH_2—$ (32). Moreover, the oxidation of tropinone with chromic acid results in the formation of resolvable (±)-tropinic acid, $C_8H_{13}O_4N$. This substance is a dicarboxylic acid and the conversion of the unresolvable tropinone into the resolvable tropinic acid clearly involves the change (XLIII) → (XLIV). Methyl tropinate methiodide on heating with aqueous sodium hydroxide is hydrolyzed and degraded to an unsaturated acid that gives pimelic acid, $HOOC—(CH_2)_5—COOH$, on hydrogenation, so tropinic acid must contain a seven-carbon chain and tropinone a seven-carbon ring (33). As tropinic acid must contain —COOH and $—CH_2COOH$, rejecting three- and four-membered ring structures, tropinic acid must have the constitution (XLV), tropinone must be (XLVI), tropine (XLVII), and atropine (XLVIII).



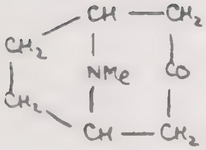
(XLIII)
TROPINONE
SYMMETRICAL



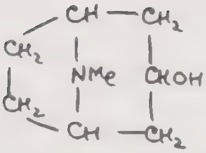
(XLIV)
(±)-TROPINIC ACID
UNSYMMETRICAL



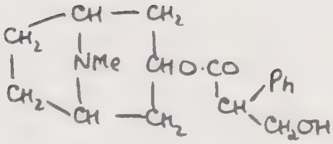
(XLV)



(XLVI)

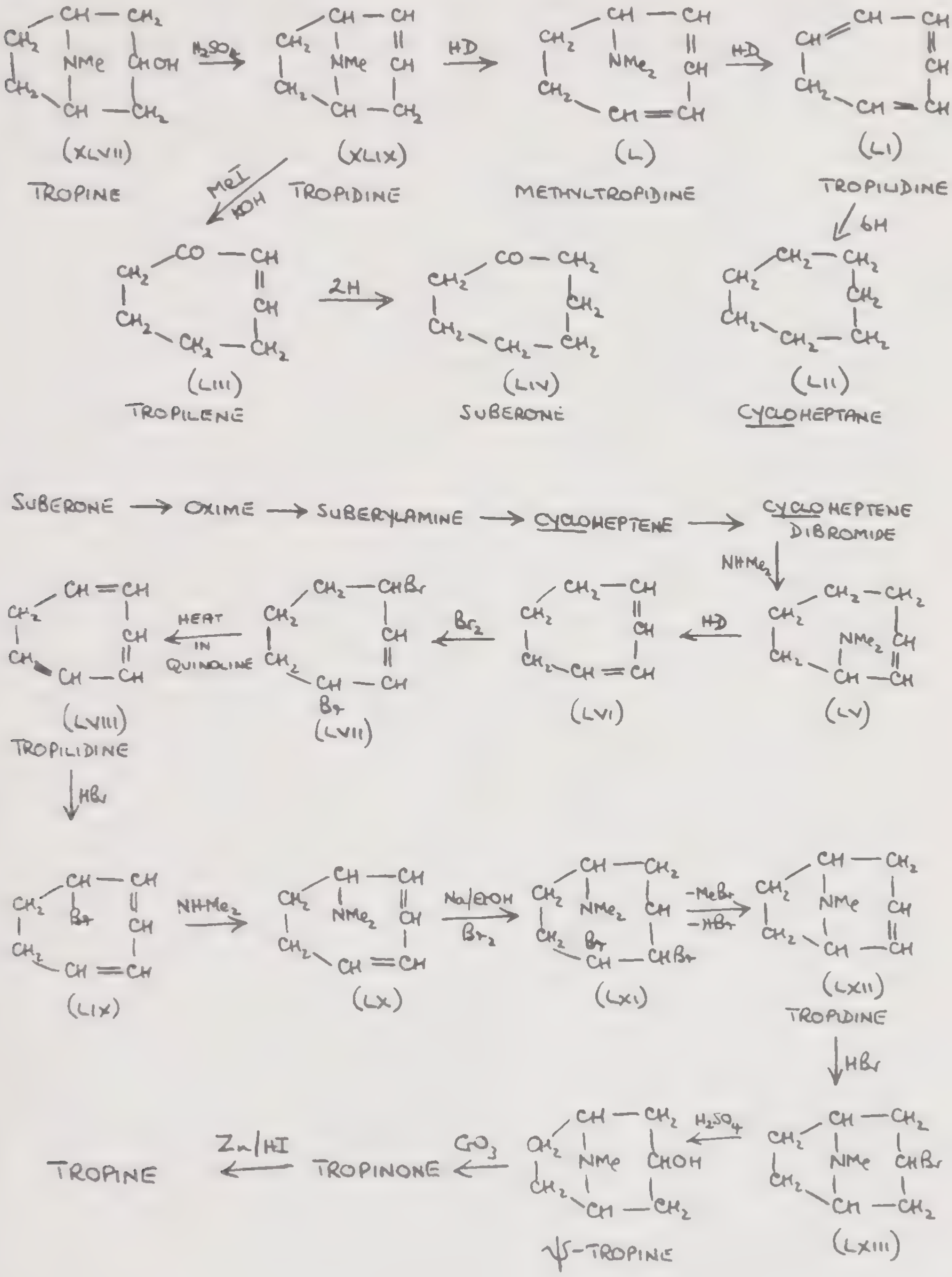


(XLVII)



(XLVIII)

The structure of tropine was confirmed by the degradations (XLVIII) ⟶ (LII) and (XLVIII) ⟶ (LIV) (15). Some of these reactions were reversed by Willstätter (35) as shown in formulas (LV) ⟶ (LXIII). The unsaturated base (LV) was prepared in stages from the ketone suberone as shown.

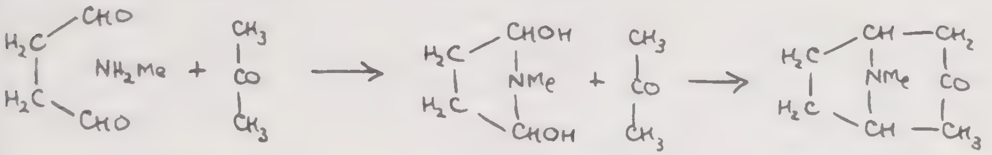

(XLVII)
TROPINE
H_2SO_4
(XLIX)
TROPIDINE
HD
(L)
METHYLTROPIDINE
HD
(LI)
TROPILIDINE
MeI
KOH
6H
(LIII)
TROPILENE
2H
(LIV)
SUBERONE
(LII)
CYCLOHEPTANE
SUBERONE → OXIME → SUBERYLAMINE → CYCLOHEPTENE → CYCLOHEPTENE DIBROMIDE
$NHMe_2$
(LV)
HD
(LVI)
Br_2
(LVII)
HEAT IN QUINOLINE
(LVIII)
TROPILIDINE
HBr
(LIX)
$NHMe_2$
(LX)
Na/EtOH
Br_2
(LXI)
-MeBr
-HBr
(LXII)
TROPIDINE
HBr
(LXIII)
H_2SO_4
ψ-TROPINE
CrO_3
TROPINONE
Zn/HI
TROPINE

However, a much simpler synthesis of tropinone, (LXIV) → (LXVI), has been devised by Robinson (21), based on the belief that tropinone might be formed in Nature through the condensation of succindialdehyde, or its equivalent with methylamine and an acetone unit, or their equivalents, in a reaction similar to the Knoevenagl reaction (in which the first step is the formation of a carbinolamine by interaction of the base and the aldehyde, followed by the reaction between this carbinolamine and the reactive methylene group of the malonic acid). When succindialdehyde, methylamine, and acetone were allowed to stand in aqueous solution for some time a small yield of tropinone was obtained.

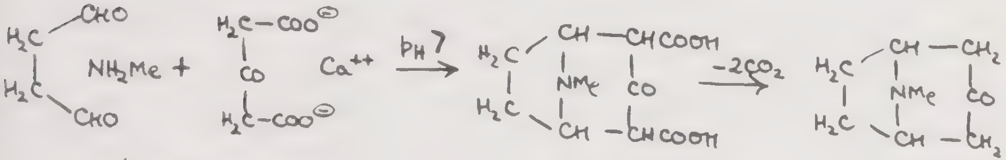
A better yield of the base can be obtained by substituting the keto-acid acetone dicarboxylic acid (obtained by the action of fuming sulfuric acid on citric acid) in the form of its calcium salt for the acetone. Decarboxylation of the product then affords tropinone, (LXVII) → (LXIX). If the half-ester of acetone dicarboxylic acid is used the product, on decarboxylation, belongs to the cocaine series, (LXX) → (LXXII). Laevulinic aldehyde, $CH_3COCH_2CH_2CHO$, has been used in place of succindialdehyde giving 1-methyltropinone (LXXIII), but γ-diketones cannot be used successfully in place of the γ-ketoaldehyde (2). The use of maleic dialdehyde leads to the production of tropenone (LXXIV) and glutaric dialdehyde affords pseudopelletierine (LXXV) (18).

The difference between tropine and ψ-tropine lies in the steric arrangement of the —CH(OH)— group; the —OH group can be on the same side (LXXVI) of the cycloheptane ring as the —NMe— bridge, or on the opposite side (LXXVII). It has recently been shown that (LXXVII) represents tropine and (LXXVI) ψ-tropine, for in nor-ψ-tropine, if the piperidine ring is configured in the boat form, there is a reasonably close approach between —NH— and —OH, and N → O and O → N migrations can occur with ease in certain derivatives. For example, *N*-benzoylnor-ψ-tropine (LXXVIII) is rapidly converted into *O*-benzoylnor-ψ-tropine (LXXIX) in acid solution, and the reverse change occurs rapidly in alkaline solution. In marked contrast *N*- and *O*-benzoylnortropine are stable (3).

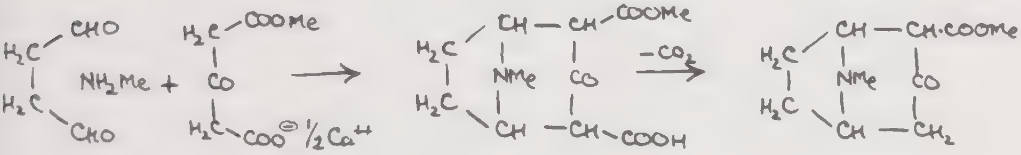
Atropine is a powerful mydriatic and this property is also found in other esters of tropine; such esters are known as tropeines, and



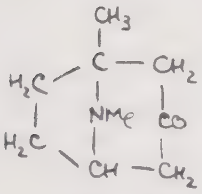
(LXIV) (LXV) (LXVI)



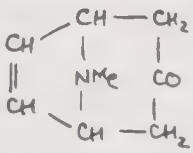
(LXVII) (LXVIII) (LXIX)



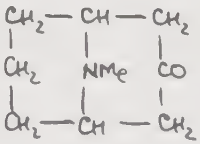
(LXX) (LXXI) (LXXII)



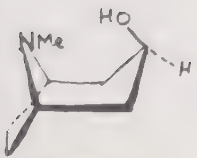
(LXXIII)



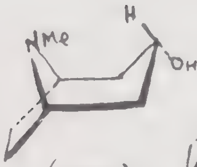
(LXXIV)



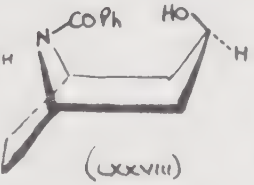
(LXXV)



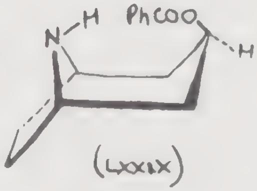
(LXXVI)



(LXXVII)



(LXXVIII)



(LXXIX)

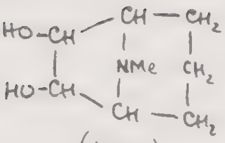
examples are atrolactyltropeine (ψ-atropine) and mandelyltropeine (homatropine). The benzoic and tiglic acid esters of ψ-tropine occur naturally as tropacocaine and tigloidine, respectively.

B. Hyoscine (Scopolamine) (LXXXV).

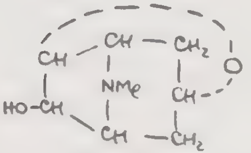
This alkaloid, which has the composition $C_{17}H_{21}O_4N$, occurs in *Scopolia japonica*, *Datura metel*, and in certain species of *Duboisia*. The free base is levorotatory, but it is readily racemized by dilute alkalis. It can be hydrolyzed by acids and alkalis to tropic acid and oscine (scopoline), $C_8H_{13}O_2N$ (11). The tropic acid can be obtained in the (−) or (±) form according to the conditions of the hydrolysis, but the oscine is always obtained in the (±) form; it was subsequently resolved by King (14).

Oscine is a tertiary base and contains one hydroxyl group and an ether oxygen atom. It can be oxidized to noroscine (scopoligenine), analogous to nortropine. The ether link can be broken by heating with hydrobromic acid (22) giving hydrobromoscopoline, which can be reduced to dihydroscopoline, containing two alcoholic hydroxyl groups. Dihydroscopoline can be oxidized to *N*-methylpiperidine-2,6-dicarboxylic acid and must therefore be (LXXX), and oscine must contain an ether oxygen atom linked to C-7; it was first suggested by King (14), and later generally accepted, that the other end of the ether linkage is at C-3, and oscine is therefore represented by (LXXXI), which may also be drawn as (LXXXII).

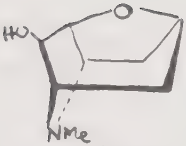
However, whereas oscine, which is not identical with its mirror image (LXXXIII), and benzoyloscine can be resolved into two optically active forms, hyoscine can only be resolved into two forms not four, and the optical activities of these two forms are due to the tropic acid residue. King (14) suggested that this is due to the fact that the basic part of the hyoscine molecule is a symmetrical unit distinct from oscine, but yielding the latter during hydrolysis. This hypothesis was confirmed when hyoscine was hydrolyzed by pancreatic lipase in a buffered solution, the product being scopine $C_8H_{13}O_2N$, which is the true basic constituent of hyoscine. Scopine, which is optically inactive and cannot be resolved, is readily converted into oscine by acids or alkalis. Scopine is represented by (LXXXIV) and hyoscine by (LXXXV). The formation of (±)-oscine



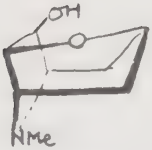
(LXXX)



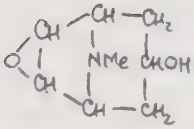
(LXXXI)



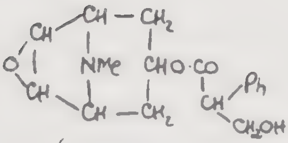
(LXXXII)



(LXXXIII)



(LXXXIV)



(LXXXV)

from the unresolvable scopine is due to the fact that as the latter is symmetrical the oxide ring can open in both ways giving (LXXXII) and (LXXXIII).

When hyoscine is oxidized with hydrogen peroxide scopinium salts, e.g., scopinium bromide (LXXXVI), are obtained, and when the latter are reduced with sodium amalgam, ψ-scopine, isomeric with scopine, is formed. ψ-Scopine does not form oscine on treatment with acids or alkalis, and this is accounted for by the structure (LXXXVII), in which, even with the piperidine ring in the "chair" form, production of a cyclic ether system is impossible.

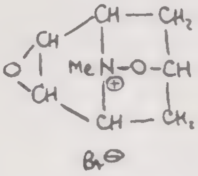
C. Cocaine (XCIII).

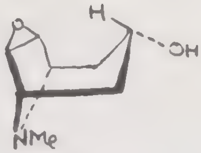
This base, which is obtained from coca leaves, has the composition $C_{17}H_{21}O_4N$, is levorotatory, and may be hydrolyzed by acids or alkalis to methyl alcohol, benzoic acid, and (–)-ecgonine, $C_9H_{15}O_3N$; only partial hydrolysis, to benzoyl-(–)-ecgonine, $C_{16}H_{19}O_4N$, and methyl alcohol, occurs when the alkaloid is boiled with water (39).

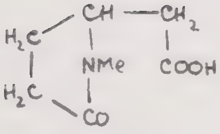
Ecgonine contains a carboxyl group and can be esterified to alkylecgonines, of which the most important is methylecgonine; this affords cocaine on benzoylation (37). The presence of a hydroxyl group in ecgonine is demonstrated by its reaction with acid chlorides and anhydrides, when acyl derivatives are formed. Ecgonine resembles tropine in many of its reactions, and oxidation with chromic acid affords tropinone, tropinic acid, and ecgoninic acid, $C_7H_{11}O_3N$, which has been shown by synthesis to have the structure (LXXXVIII). Ecgonine must therefore be either the hydroxy-acid (LXXXIX) or the isomeric (XC). It was shown to have the structure (LXXXIX) by dehydration, hydrogenation, and Hofmann degradation of the amide to the amine (XCI), which is isomeric, but not identical, with tropylamine and ψ-tropylamine (XCII). Cocaine must therefore have the constitution (XCIII).

For the synthesis of ecgonine, and therefore of cocaine, by Robinson's method, see above under "tropinone."

Other methylacylecgonines occur in the coca leaf, and cocaine is usually prepared by the hydrolysis of the total coca alkaloids followed by methylation and benzoylation of the resulting ecgonine.


(LXXXVI)


(LXXXVII)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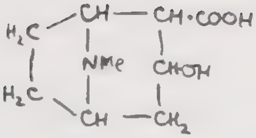
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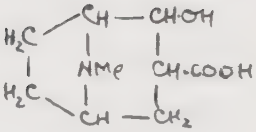
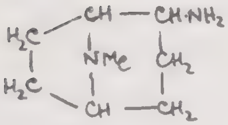

(XC)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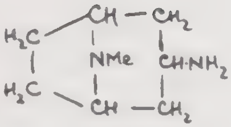
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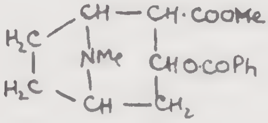
(XCIII)

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CHAPTER 2

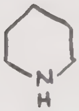
ALKALOIDS OF THE PYRIDINE: PIPERIDINE GROUP

1. SIMPLE DERIVATIVES OF PIPERIDINE

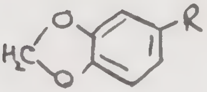
A. Piperine (IV).

This alkaloid, which has the composition $C_{17}H_{19}O_3N$, occurs in the kernel of the ripe fruit (white pepper) and in the unripe fruit (black pepper) of *Piper nigrum* (22). It may be hydrolyzed to piperidine (I) (1,7) and piperic acid (65,66), which may be oxidized by permanganate to the aldehyde piperonal (II, R = CHO), piperonylic acid (II, R = COOH), tartaric acid, and oxalic acid (16,18), and may be catalytically reduced to tetrahydropiperic acid (6). These facts suggest that piperic acid has the structure (III) and this was confirmed by synthesis from piperonal, which was condensed with acetaldehyde to give (II, $R = CH{=}CH \cdot CHO$) and this afforded piperic acid (III) on condensation with acetic anhydride and sodium acetate (39). Piperine may be prepared by treating piperidine (I) with the acid chloride of piperic acid (59) and hence the alkaloid must have the structure (IV).

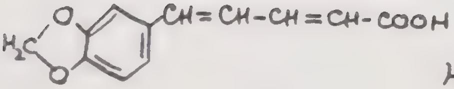
The stereochemical arrangement of groups about the double bonds in piperic acid is *trans* : *trans*, i.e., as in (V). Chavicine, an isomer of piperine, also occurring in pepper, may be hydrolyzed to piperidine and isochavicinic acid (51). This acid is isomeric with piperic acid and both give the same tetrahydro derivative; it has either a *cis* : *cis* (VI) or a *cis* : *trans* (VII) arrangement of groups.



(I)



(II)



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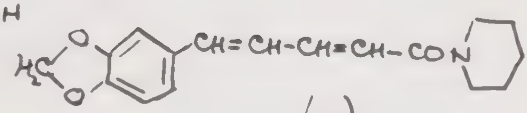

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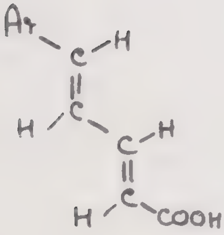
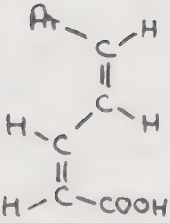


(V)



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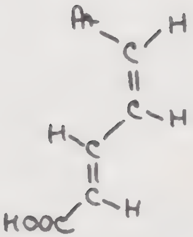


(VII)

B. Arecoline (IX).

Arecoline, which may be isolated from betel nut, has the composition $C_8H_{13}O_2N$, and contains one —COOMe group and one —NMe— group. It may be hydrolyzed to the acid arecaidine, $C_7H_{11}O_2N$, which also occurs naturally, and this can be esterified with methanol to give arecoline (32). Arecaidine may be reduced to dihydroarecaidine and so must contain one double bond. Methyl nicotinate methiodide (VIII) on reduction with zinc and hydrochloric acid affords an *N*-methyltetrahydronicotinic acid identical with arecaidine (32). As arecaidine is optically inactive and as neither the natural nor the synthetic material can be resolved it must have the structure (IX) or (X), as alternatives such as (XI) contain an asymmetric carbon atom. The structure (IX) was shown to be correct by the synthesis (XII) ⟶ (XV) ⟶ (IX) (79).

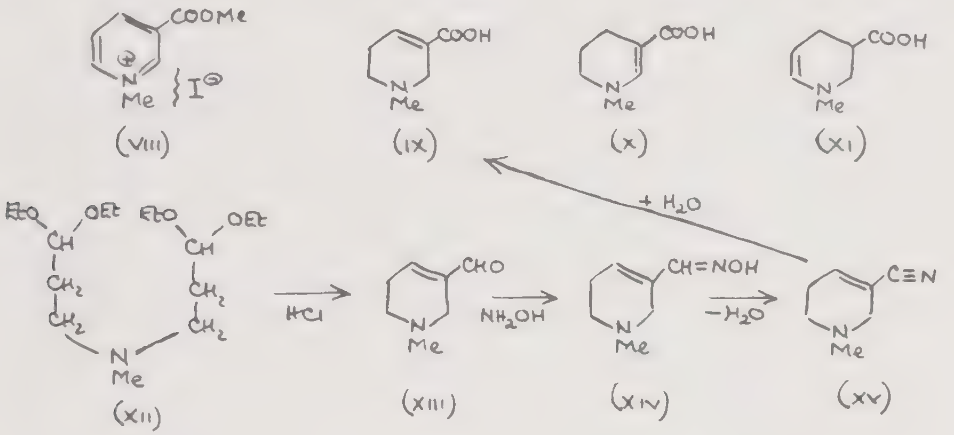
C. Guvacine.

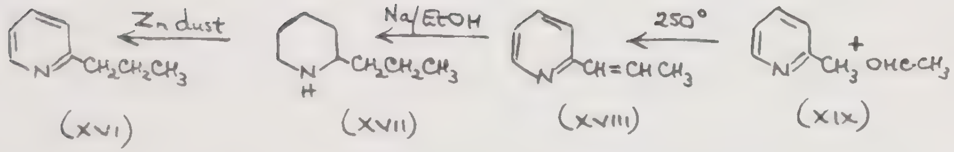
This alkaloid, $C_6H_9O_2N$, is *N*-desmethylarecaidine, and can be converted into arecaidine methyl betaine by the action of methyl iodide in methanol (72,73).

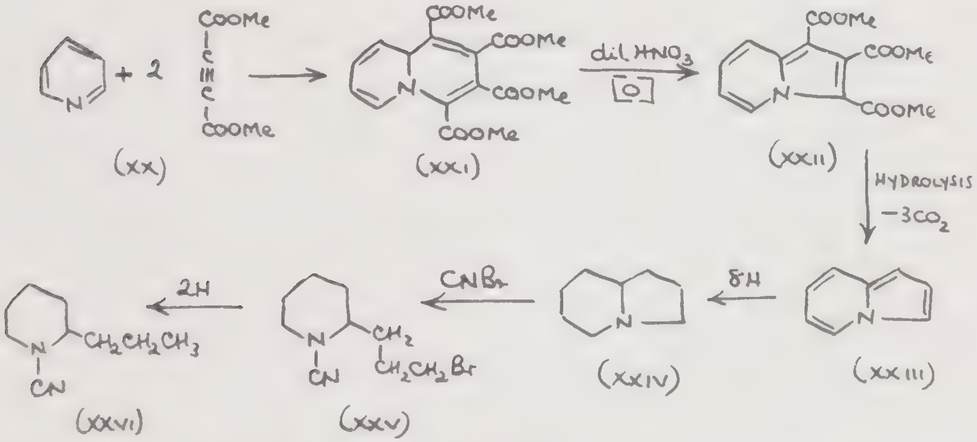
D. Coniine (XVII).

Coniine, which has the composition $C_8H_{17}N$, is the principal toxic substance present in hemlock (*Conium maculatum*). On distillation with zinc dust it loses six hydrogens giving conyrine $C_8H_{11}N$ (26), which on oxidation affords pyridine-2-carboxylic acid (26). As conyrine is not identical with 2-isopropylpyridine prepared by synthesis (36) it must be 2-*n*-propylpyridine (XVI), and coniine must therefore be 2-*n*-propylpiperidine (XVII). This view was confirmed by the synthesis of coniine (XIX) ⟶ (XVIII) ⟶ (XVII) (37). Other syntheses have since been recorded (17,35,38) and one such synthesis is outlined in formulas (XX) ⟶ (XXVI) ⟶ (XVII) (15).

Exhaustive methylation of coniine affords the nitrogen-free substance conylene, C_8H_{14} (67), which may be reduced to *n*-octane, which is also obtained by the reduction of the alkaloid with red phosphorus and hydriodic acid (27).


COOMe
N
Me
$I^{\ominus}$
(VIII)
COOH
N
Me
(IX)
COOH
N
Me
(X)
COOH
N
Me
(XI)
+ H_2O
EtO
OEt
EtO
OEt
CH
CH
CH_2
CH_2
CH_2
CH_2
N
Me
(XII)
HCl
CHO
N
Me
(XIII)
NH_2OH
CH=NOH
N
Me
(XIV)
$-H_2O$
C≡N
N
Me
(XV)


Zn dust
N
$CH_2CH_2CH_3$
(XVI)
Na/EtOH
N
H
$CH_2CH_2CH_3$
(XVII)
250°
N
CH=CH CH_3
(XVIII)
+
N
CH_3 OHC·CH_3
(XIX)


N
+ 2
COOMe
C
C
COOMe
(XX)
COOMe
COOMe
COOMe
COOMe
N
(XXI)
dil. HNO_3
[O]
COOMe
COOMe
COOMe
N
(XXII)
HYDROLYSIS
$-3CO_2$
N
(XXIII)
8H
N
(XXIV)
CNBr
N
CN
CH_2
CH_2CH_2Br
(XXV)
2H
N
CN
$CH_2CH_2CH_3$
(XXVI)

E. Conhydrine (XXVII).

This base, $C_8H_{17}ON$, is a hydroxyconiine, and it may be converted, through the iodide, into coniine. The hydroxyl group must be in the side chain, since the base may be oxidized to piperidine-2-carboxylic acid. This group cannot be at the end of the side chain since attempts to oxidize the base to 2-piperidylpropionic acid have never succeeded; of the two possible structures for conhydrine, (XXVII) and (XXVIII), the former has been shown to be correct by the synthesis of the related ketone (XXIX) (23); (XXVIII) has also been synthesized and found to be different from the natural alkaloid (17).

F. The Coniceines.

These bases are all dehydroconiines; only the γ-isomer occurs naturally, all the others are prepared from natural alkaloids of hemlock.

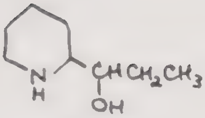
γ-Coniceine, $C_8H_{15}N$, is a mono-unsaturated base that gives (±)-coniine on hydrogenation and 2-*n*-propylpyridine on dehydrogenation. It has been allotted the structure (XXX) (42) and this has been confirmed by the synthesis (XXXI) → (XXX) (20).

α-Coniceine may be prepared by the action of fuming hydrochloric acid on conhydrine; its structure has never been elucidated satisfactorily, but it may be (XXXII).

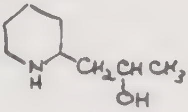
β-Coniceine is the main product of the dehydration of conhydrine. It is optically active and may be reduced to (–)-coniine; it therefore has the structure (XXXIII) and this has been confirmed by synthesis (46).

δ-Coniceine may be obtained by the action of sulfuric acid on bromoconiine (41). It is a saturated bicyclic base and has the constitution (XXXIX); it has been synthesized by the route (XXXIV) → (XXXIX) (47).

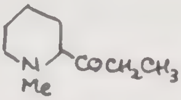
ε-Coniceine, believed to be a mixture of two stereoisomerides of structure (XXXII), is obtained by the action of hydriodic acid on conhydrine.



(XXVII)



(XXVIII)



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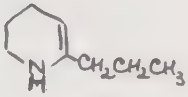
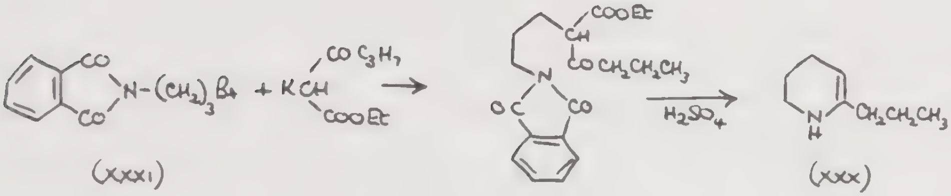
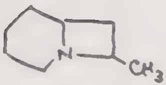


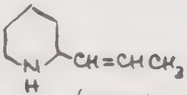
(XXX)



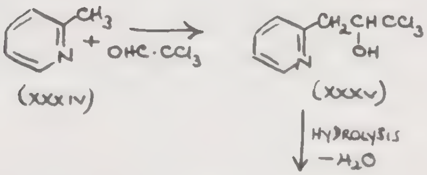
(XXXI) (XXX)



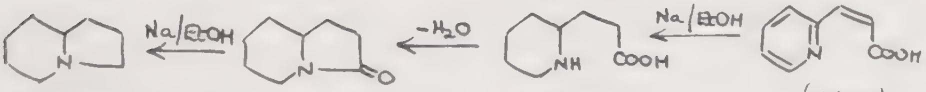
(XXXII)



(XXXIII)



(XXXIV) (XXXV)



(XXXIX) (XXXVIII) (XXXVII) (XXXVI)

G. Pelletierine (XL, R = CHO).

This base, isolated from pomegranate root bark, has the composition $C_8H_{15}ON$, and contains one —NH— group and one aldehyde group. The presence of the —CHO group was demonstrated by the dehydration of pelletierine oxime to a nitrile that afforded β-2-piperidylpropionic acid (XL, R = COOH) on hydrolysis (24,47). Pelletierine hydrazone on reduction by the Wolff-Kishner method affords (±)-coniine (XVII). These results show that pelletierine must have the structure (XL, R = CHO). Although no synthesis of the alkaloid has been recorded pelletierine acetal has been synthesized by the route shown, (XLI) → (XLII) → (XLIII) (68).

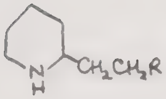
H. Methylisopelletierine (XLIV, R = Me).

This base, $C_9H_{17}ON$, is the piperidine analog of hygrine. It is a ketone and the hydrazone gives (±)-*N*-methylconiine on reduction; on oxidation the alkaloid furnishes 1-methylpiperidine-2-carboxylic acid (23). It has been shown to have the constitution (XLIV, R = Me) by synthesis from α-(2-pyridyl)-propan-β-ol, which was catalytically hydrogenated and subsequently oxidized to the ketone (25,49). The alkaloid isopelletierine may be methylated to methylisopelletierine and has the structure (XLIV, R = H).

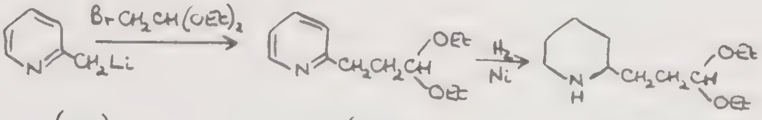
I. Pseudopelletierine (XLVII).

This alkaloid, $C_9H_{15}ON$, forms an oxime and a dipiperonylidine and dibenzylidine derivative (50,53), it can also be reduced to a secondary alcohol (8) and hence must contain the system $—CH_2—CO—CH_2—$. The reactions of pseudopelletierine, which has been renamed *N*-methylgranatonine, are very similar to those of tropinone. The related secondary alcohol, *N*-methylgranatoline, may be dehydrated to the olefin *N*-methylgranatenine, which may be reduced to *N*-methylgranatanine, also obtainable by the electrolytic reduction of *N*-methylgranatonine (55).

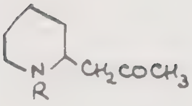
N-methylgranatoline may be oxidized to granatic acid, $C_9H_{15}O_4N$, a reaction analogous to the oxidation of tropine to tropic acid and involving the change $—CH_2—CO—CH_2— \rightarrow —COOH + HOOC—CH_2—$. The methyl ester of granatic acid may be exhaustively methylated in stages to dimethyl *N*-dimethylgranatenate (XLV) and homopiperylenedicarboxylic acid (XLVI) and the last of



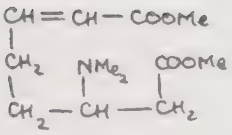
(XL)



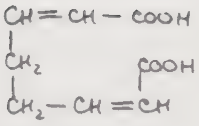
(XLI) (XLII) (XLIII)



(XLIV)



(XLV)



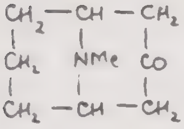
(XLVI)

these may be hydrogenated to suberic acid, $HOOC—(CH_2)_6—COOH$ (52). Pseudopelletierine must thus contain an eight-carbon ring.

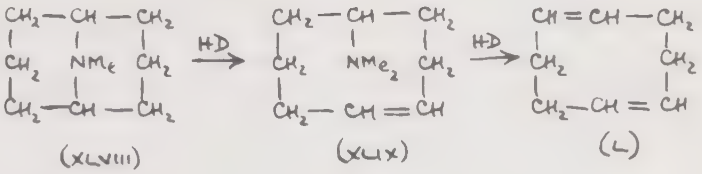
The close similarity between tropinone and pseudopelletierine finally led to the proposal of the structure (XLVII) for the latter (54). This is supported by the results of exhaustive methylation of *N*-methylgranatanine (XLVIII), which leads successively to the base (XLIX) and the diene (L) (21,77). Exhaustive methylation of *N*-methylgranatenine (LI) affords cyclo-octatriene (LII) as final product, and the bromination of this results in the addition of bromine at the ends of the conjugated system giving (LIII) which is converted into cyclo-octatetraene (LIV) on dehydrobromination (75,76). This preparation of cyclo-octatetraene has been repeatedly questioned, but has been recently vindicated by repetition (13), the product being identical with the cyclic polyolefin synthesized by Reppe by the polymerization of acetylene (58).

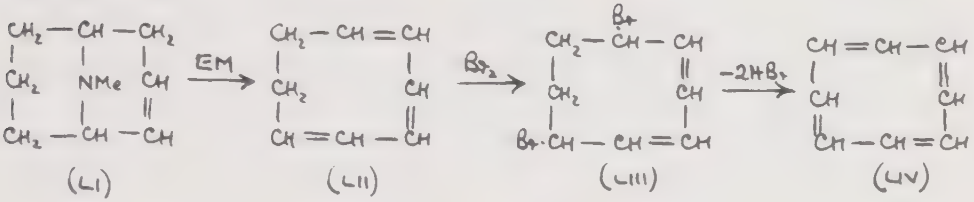
It will be seen from (XLVII) and (XLIV, R = Me) that pseudopelletierine bears the same relationship to methylisopelletierine as tropinone does to hygrine.

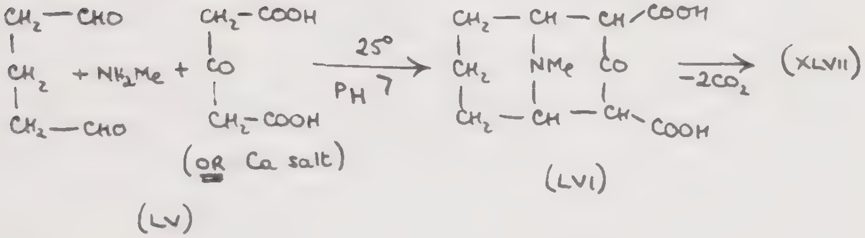
Pseudopelletierine (XLVII) has been synthesized by an extension of the Robinson tropinone synthesis (see Chapter 1) as shown in formulas (LV), (LVI), and (XLVII) (50,61). A number of analogous compounds, e.g., the bases (LVII) and (LVIII), may be synthesized in the same way from the appropriate aldehyde (4,5).

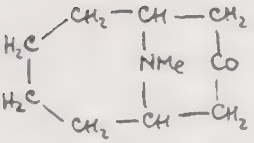


(XLVII)

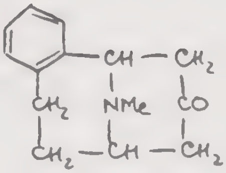








(LVII)



(LVIII)

2. THE LOBELIA ALKALOIDS

The alkaloids of *Lobelia* species may conveniently be dealt with briefly in three groups.

A. Lobeline Group (LXIII, R = Me, X = Z = Ph · CO).

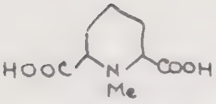
All the alkaloids of this group give acetophenone when heated in the presence of a catalyst. All are derivatives of piperidine and most are ketonic. The oxidation of the alkaloid lobelanine yields benzoic acid and 1-methylpiperidine-2,6-dicarboxylic acid (LIX) and the Beckmann transformation of lobelanine dioxime affords the dianilide (LX) of 1-methylpiperidine-2,6-diacetic acid (69). The exhaustive methylation of lobelanine furnishes, after two steps, a nitrogen-free diene (LXI) that on hydrogenation is converted into 1,7-dibenzoylheptane.

Lobelanine may thus be allotted the structure (LXIII, R = Me, X = Z = Ph · CO). The structures of the other members of this subgroup are as follows; norlobelanine (LXIII, R = H, X = Z = Ph · CO); lobeline (LXIII, R = Me, X = Ph · CO, Z = Ph · CH (OH)); lobelanidine (LXIII, R = Me, X = Z = Ph · CH (OH)).

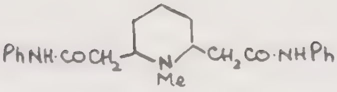
Lobelanine has been synthesized by use of the same general method as that on which the Robinson tropinone synthesis is based. A mixture of glutaric dialdehyde, benzoylacetic acid, and methylamine hydrochloride (LXII) was allowed to stand at 25° at pH 4–5 for forty hours (61). Other members of the group have also been synthesized (60,70).

B.. Lelobine Group (LXIII, R = Me, X = Et · CO, Z = Ph · CO).

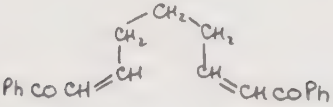
This group contains minor alkaloids isolated from residues obtained from the extraction of the alkaloids of the lobeline group. They are of the same structural type as the alkaloids of the first group, but have an ethyl group in place of one of the phenyl groups, and may in general be represented by the formula (LXIII). Lelobanidine has the structure (LXIII, R = Me, X = Et · CH (OH), Z = Ph · CH (OH)); norlelobanidine (LXIII, R = H, X = Et · CH (OH), Z = Ph · CH (OH)); lelobanine (LXIII, R = Me, X = Et · CO, Z = Ph · CO).



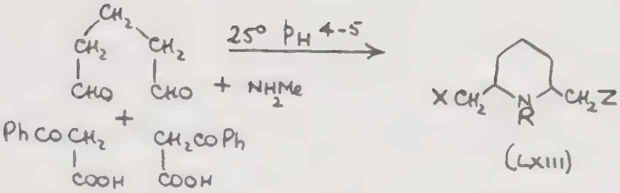
(LIX)



(LX)



(LXI)



(LXII)

(LXIII)

C. Lobinine Group (LXIV, X = Et · CO, Z = Ph · CO).

This comprises a second group of minor alkaloids, all of which are unsaturated. Wieland (71) placed the double bond as shown in (LXIV), and the group consists of lobinine and isolobinine, stereoisomers, (LXIV, X = Et · CH(OH), Z = Ph · CO); lobinanine (LXIV, X = Et · CO, Z = Ph · CO); lobinanidine (LXIV, X = Et · CH(OH), Z = Ph · CH(OH)).

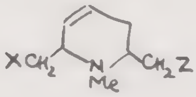
For a detailed discussion of the lobelia alkaloids see refs. 22 and 48.

3. THE LUPINE ALKALOIDS

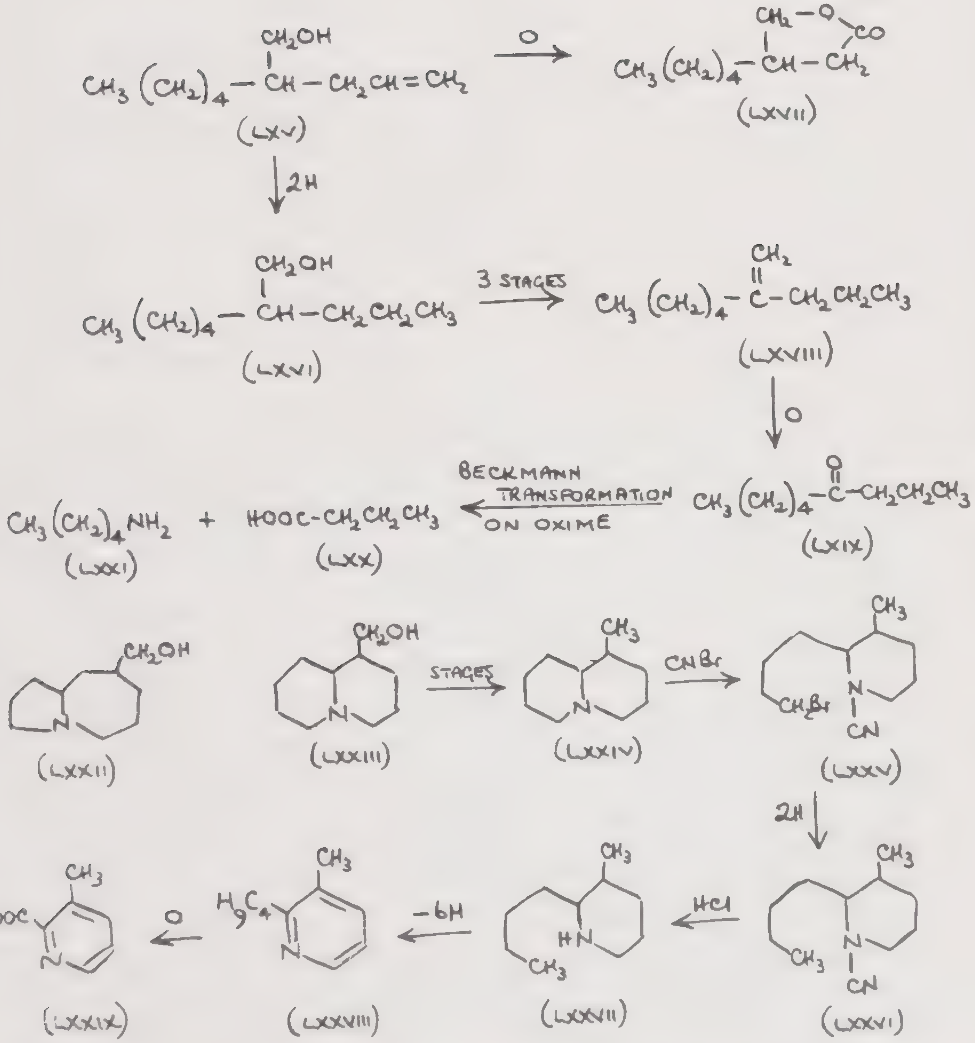
These alkaloids, which occur in a wide variety of leguminous plants, may conveniently be divided into three groups, and one member of each group will be taken for discussion.

A. The Lupinine Group (LXXIII).

Lupinine itself has the composition $C_{10}H_{19}ON$. It contains a primary alcoholic group and a tertiary nitrogen atom; this nitrogen atom must be common to two rings as three stages are necessary for its elimination by exhaustive methylation (74). When exhaustive methylation is carried out with hydrogenation at each stage except the last, the alcohol (LXV) is obtained, and this may be hydrogenated to (LXVI) and oxidized to the lactone (LXVII). All these products are optically active, but the activity disappears when (LXVI) is converted into the olefin (LXVIII). This olefin may be oxidized to the ketone (LXIX), the oxime of which, when subjected to the Beckmann transformation, affords an amide that gives *n*-amylamine (LXXI) and *n*-butyric acid (LXX) on hydrolysis (33). These reactions unambiguously fix the structure of the ketone (LXIX) and the alcohol (LXV). As lupinine contains no C—Me group, the two ends, and one other carbon atom, of the eight-carbon chain of (LXV) must be attached to the nitrogen atom in the alkaloid, and consequently only two structures, (LXXII) and (LXXIII), may reasonably be advanced for lupinine. Of these two structures (LXXIII) was shown to be that of lupinine by the sequence of reactions (LXXIII) → (LXXIX) (78). Lupinine has been synthesized by the route shown, (LXXX) → (LXXXV) (11), with final resolution of the product (12).

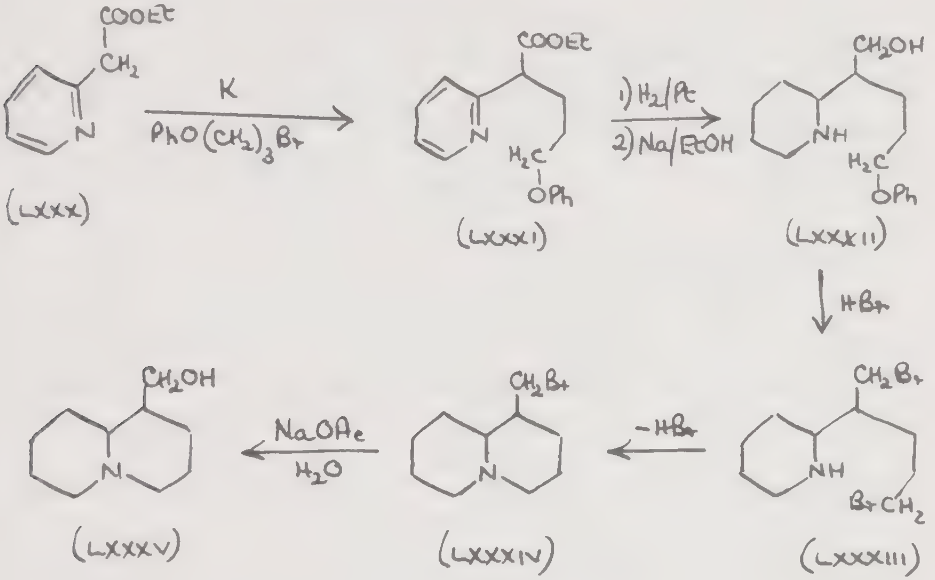

XCH2
N
Me
CH2Z

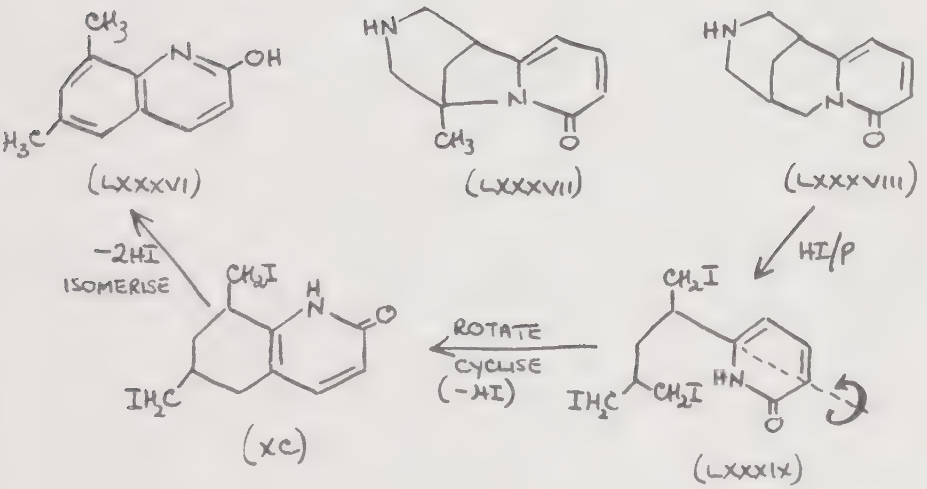
(LXIV)


CH3(CH2)4—CH(CH2OH)—CH2CH=CH2
(LXV)
O
CH3(CH2)4—CH—CH2 (CH2—O—CO)
(LXVII)
2H
CH3(CH2)4—CH(CH2OH)—CH2CH2CH3
(LXVI)
3 STAGES
CH3(CH2)4—C(=CH2)—CH2CH2CH3
(LXVIII)
O
CH3(CH2)4—CO—CH2CH2CH3
(LXIX)
BECKMANN TRANSFORMATION ON OXIME
CH3(CH2)4NH2
(LXXI)
+
HOOC-CH2CH2CH3
(LXX)
CH2OH
N
(LXXII)
CH2OH
N
(LXXIII)
STAGES
CH3
N
(LXXIV)
CNBr
CH3
CH2Br
N
CN
(LXXV)
2H
CH3
CH3
N
CN
(LXXVI)
HCl
CH3
HN
CH3
(LXXVII)
−6H
CH3
H9C4
N
(LXXVIII)
O
CH3
HOOC
N
(LXXIX)

B. The Cytisine Group (LXXXVIII).

The alkaloid cytisine, which is found in the seeds of laburnum and various species of broom, has the composition $C_{11}H_{14}ON_2$ and contains one feebly basic tertiary nitrogen atom and one basic —NH— group; the oxygen atom is inert. It may be reduced electrolytically to tetrahydrodesoxycytisine, $C_{11}H_{20}N_2$. Numerous reactions, e.g., nitration and bromination, lead to the conclusion that the alkaloid contains an aromatic nucleus with two easily replaced hydrogen atoms. When cytisine is heated with hydrogen iodide and red phosphorus at 225° cytisoline (LXXXVI) is obtained (19), and several formulas based on the quinoline nucleus were suggested before Ing (29) suggested that the aromatic reactions of cytisine can be satisfactorily explained by assuming the presence of an α-pyridone ring in the alkaloid. Ing suggested that the basic quinoline structure is not present in cytisine and that the alkaloid was either (LXXXVII) or (LXXXVIII). The second of these structures has since been shown to correspond to cytisine; oxidation studies on *N*-methylcytisine have provided satisfactory evidence on this point.


(LXXX)
K
PhO(CH2)3Br
(LXXXI)
1) H2/Pt
2) Na/EtOH
(LXXXII)
HBr
(LXXXIII)
−HBr
(LXXXIV)
NaOAc
H2O
(LXXXV)

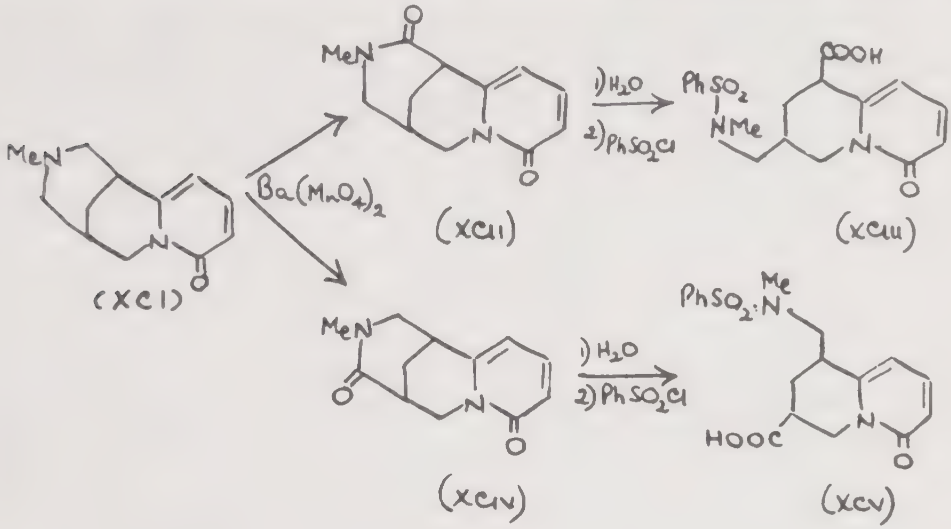

(LXXXVI)
(LXXXVII)
(LXXXVIII)
HI/P
(LXXXIX)
ROTATE
CYCLISE
(−HI)
(XC)
−2HI
ISOMERISE

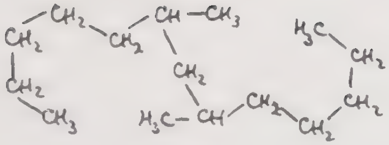
The two products of oxidation, (XCII) and (XCIV), of *N*-methylcytisine (XCI) on subsequent hydrolysis and benzoylation gave the acids (XCIII) and (XCV), respectively, and of these (XCIII), like derivatives of pyridine-2-acetic acid, was easily decarboxylated (30). The base cytisoline (LXXXVI) presumably arises from cytisine as shown (LXXXVIII) → (XC) → (LXXXVI).

C. The Lupanine Group (XCVII).

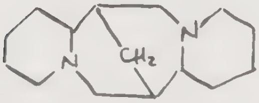
The simplest alkaloid of this group is sparteine, which may be obtained from *Cytisus* species. It has the composition $C_{15}H_{26}N_2$ and contains two tertiary nitrogen atoms, both of which are common to two rings. The alkaloid contains no double bonds and the molecular formula accordingly indicates the presence of four rings in the molecule, which also contains no C—Me group. Exhaustive methylation of sparteine, with hydrogenation at each stage, affords as final product 6,8-dimethyltridecane (XCVI) (34), but the structure of this material only became clear after the constitution of sparteine had been shown to be (XCVII). This structure for the alkaloid was suggested by Clemo and Raper (9) after work by Ing (31). It may be regarded as an almost double lupinine.

Sparteine has been synthesized by the methods shown, (XCVIII) ⟶ (C) (10); (XCVIII) ⟶ (CI) → (CII) → (C) (44,45); and (XCVIII) ⟶ (CI) ⟶ (CIII) ⟶ (C) (62). An elegant synthesis, particularly interesting from the point of view of the possible mode of biogenesis

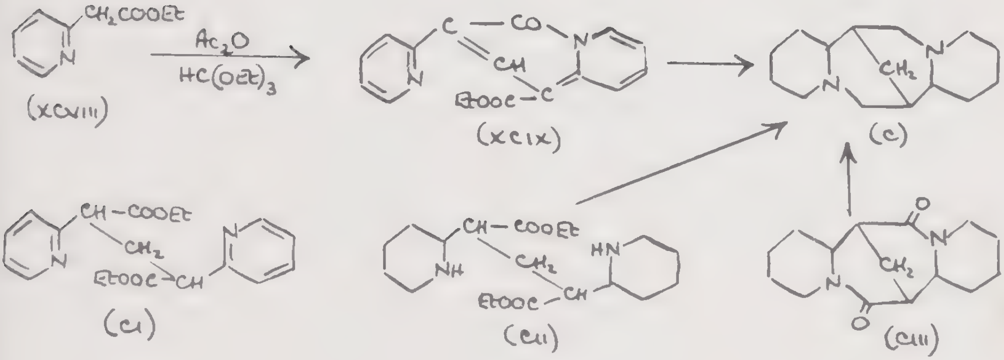

(XCI)
Ba(MnO4)2
(XCII)
1) H2O
2) PhSO2Cl
(XCIII)
(XCIV)
1) H2O
2) PhSO2Cl
(XCV)



(XCVI)



(XCVII)


(XCVIII)
Ac2O
HC(OEt)3
(XCIX)
(C)
(CI)
(CII)
(CIII)

of the alkaloid, was recently achieved by Anet, Hughes, and Ritchie (2,3) as shown in formulas (CIV) ⟶ (CV) ⟶ (XCVII).

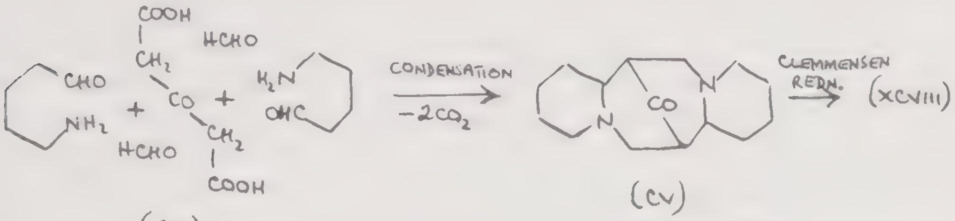
Other alkaloids of this group are lupanine (CVI) and anagyrine (CVII); matrine (CVIII) has an unusual arrangement of the two fused ring systems.

For a detailed treatment of the lupin alkaloids see refs. 22 and 43.

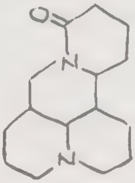
4. THE TOBACCO ALKALOIDS

A. Nicotine (CIX).

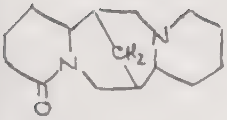
Nicotine, $C_{10}H_{14}N_2$, is the chief alkaloid of tobacco and of *Nicotiana* species in general. It is a colorless levorotatory oil giving dextrorotatory salts. When it is oxidized with chromic acid it yields an amino acid, $C_6H_5O_2N$, which may be decarboxylated to pyridine (28). This acid, nicotinic acid, was subsequently shown to be pyridine-β-carboxylic acid (40). Nicotine is therefore a 3-substituted pyridine and the molecular formula shows that the substituent must be saturated. The alkaloid forms a crystalline addition compound with zinc chloride, and when this is heated with lime pyridine, pyrrole and methylamine are obtained, suggesting that the structure may be (CIX), and this was supported by the degradation of the alkaloid to *N*-methylproline, (CIX) ⟶ (CXIII), the oxidation of dibromocotinine (CXIV) to nicotinic acid, malonic acid and methylamine, (CXIV) ⟶ (CXV), and the reductive hydrolysis of dibromocotinine to methylamine and the dihydroxy-acid (CXVI) (57).



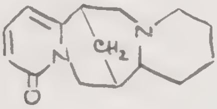
(CIV)



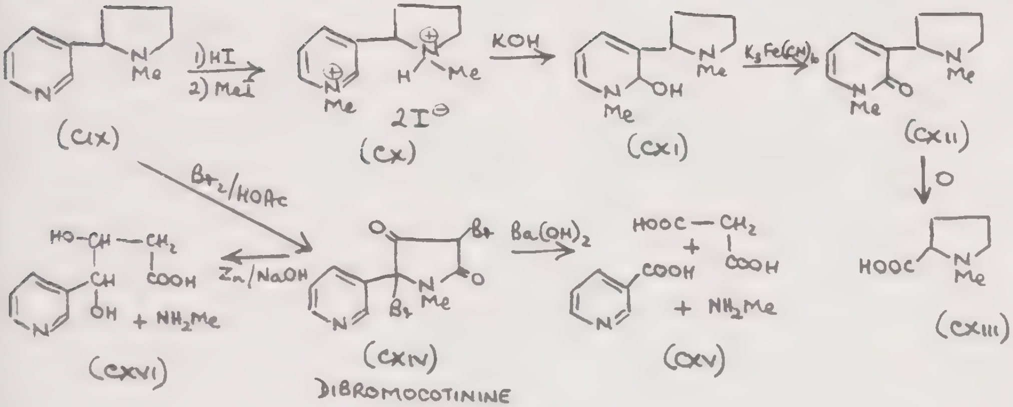
(CVIII)



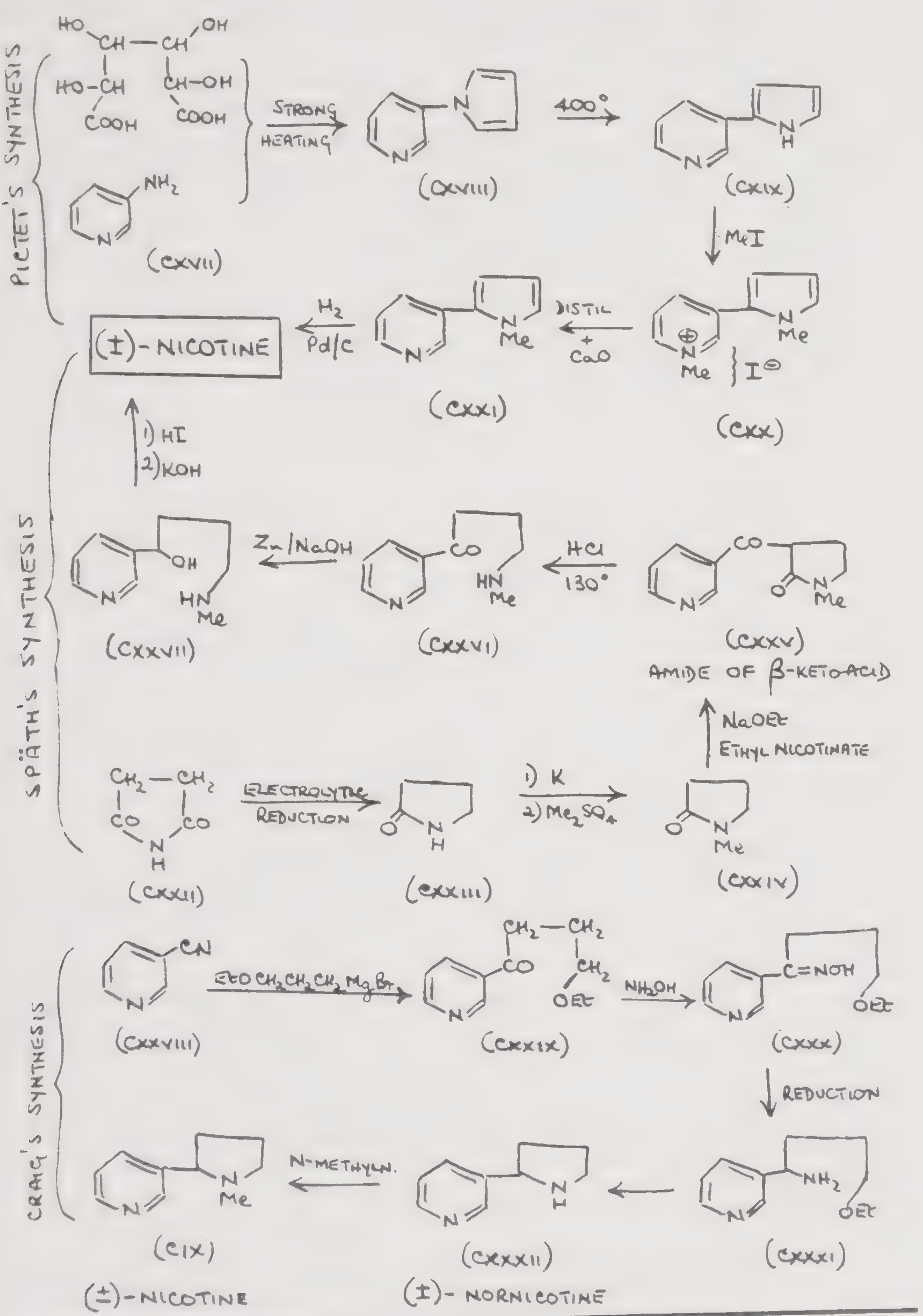
(CVI)



(CVII)



This structure was finally confirmed by synthesis. Three syntheses of nicotine have been recorded and are given in formulas (CXVII) ⟶ (CXXI) ⟶ (CIX) (56,64); (CXXII) ⟶ (CXXVII) ⟶ (CIX) (63), and (CXXVIII) ⟶ (CXXXII) ⟶ (CIX) (14). Of these the first involves a rearrangement on passing the intermediate (CXVIII) through a hot tube at 400 ° and cannot therefore be regarded as unambiguous, but the other two are structurally specific.


PICTET'S SYNTHESIS
HO–CH–CH–OH
HO–CH CH–OH
COOH COOH
STRONG HEATING
(CXVII)
(CXVIII)
400°
(CXIX)
MeI
(CXX)
I⊖
DISTIL + CaO
(CXXI)
H2 Pd/C
(±)-NICOTINE
SPÄTH'S SYNTHESIS
1) HI
2) KOH
Zn/NaOH
(CXXVII)
HCl 130°
(CXXVI)
(CXXV)
AMIDE OF β-KETO-ACID
NaOEt
ETHYL NICOTINATE
ELECTROLYTIC REDUCTION
(CXXII)
(CXXIII)
1) K
2) Me2SO4
(CXXIV)
CRAIG'S SYNTHESIS
(CXXVIII)
EtO CH2CH2CH2 MgBr
(CXXIX)
NH2OH
(CXXX)
REDUCTION
(CXXXI)
(CXXXII)
N-METHYLN.
(CIX)
(±)-NICOTINE
(±)-NORNICOTINE

B. Anabasine (CXXXIII).

This is one of the minor alkaloids of tobacco, but it is the chief alkaloid of the Asiatic plant *Anabasis aphylla*. It has the constitution of β-2-piperidylpyridine (CXXXIII).

Other alkaloids of this type are anatabine (CXXXIV), *N*-methylanabasine, and *N*-methylanatabine.

C. Tobacco Smoke Alkaloids.

Tobacco smoke contains several bases not found in the tobacco leaf; of these myosmine (CXXXV) and poikiline (CXXXVI) may be cited. For a detailed discussion of these bases see ref. 48.

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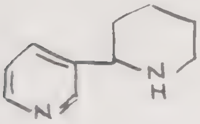
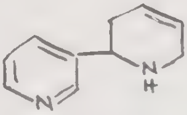
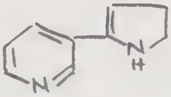


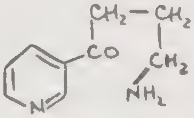
(CXXXIII)



(CXXXIV)



(CXXXV)



(CXXXVI)

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CHAPTER 3

ALKALOIDS OF THE ISOQUINOLINE GROUP: I

1. PHENYLETHYLAMINES AND SIMPLE ISOQUINOLINES

A. Mescaline (IV).

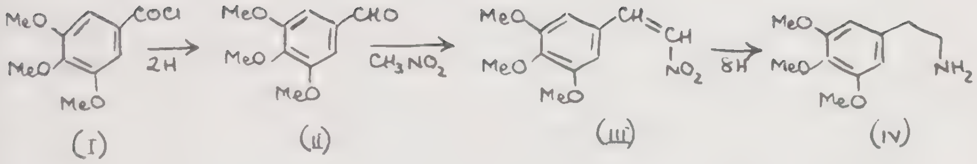
Though not strictly a member of the isoquinoline group this alkaloid is conveniently considered here. It is the principal alkaloid of the cactus *Anhalonium Lewinii*, the flowering heads of which have been imported into Europe under the name of "mescal buttons." It has the composition $C_{11}H_{17}O_3N$ and contains three methoxyl groups and one aliphatic primary amino group. It is a derivative of β-phenylethylamine, has the structure (IV), and was synthesized by Spāth (51) as shown in formulas (I) ⟶ (IV). Several other syntheses have also been recorded (18,40,49,50).

In humans mescaline is reputed to produce vivid colored halucinations and a feeling of well being; it is generally reported to produce no after effects.

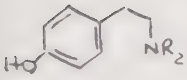
Other alkaloids of the mescaline type are tyramine (V, R = H), hordenine (V, R = Me), candicine (hordenine methohydroxide), and trichocereine (*N*-dimethylmescaline) (40).

B. Anhalonidine (X, R = H).

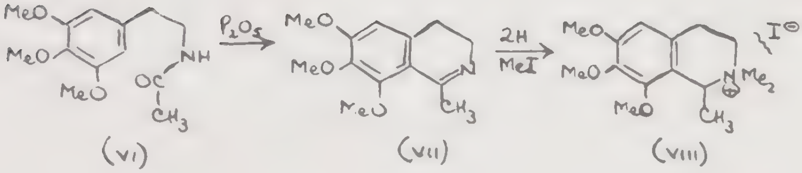
This base, a true isoquinoline alkaloid, also occurs in *Anhalonium Lewinii.* The basic structure of the alkaloid was revealed by Spāth's synthesis of *O:N*-dimethylanhalonidine methiodide (VIII) from *N*-acetylmescaline (VI) as shown in formulas (VI) ⟶ (VIII) (52).



(I) (II) (III) (IV)



(V)



(VI) (VII) (VIII)

Anhalonidine was subsequently synthesized from 3-acetoxy-4,5-dimethoxy-*N*-acetylphenylethylamine (IX) (53); it has the structure (X, R = H), the position of the hydroxyl group being confirmed by oxidation of *O*-ethyl-*N*-methylanhalonidine (the ethyl ether of pellotine (X, R = Me)) to 3-ethoxy-4,5-dimethoxyphthalic acid (XI) (57).

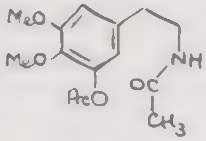
Several other cactus alkaloids are very closely related to anhalonidine, see ref. 41.

C. Cotarnine (XX) and Hydrastinine (XXXIII).

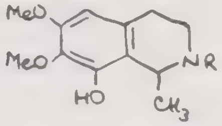
These two substituted tetrahydroisoquinolines do not occur naturally, but are easily obtained by the acid hydrolysis and oxidation of narcotine and hydrastine (see below) and are conveniently considered at this point.

Cotarnine, $C_{12}H_{15}O_4N$, contains one methoxyl group, one methylenedioxy group, and one —NMe— group. On oxidation with permanganate it gives cotarnic acid, $C_8H_6O_3(COOH)_2$, which readily forms an anhydride and was quickly recognized as a derivative of phthalic acid (43); hydriodic acid and red phosphorus convert cotarnic acid into gallic acid (XII) (44). Cotarnine reacts with aniline as if it were an aromatic aldehyde, giving an anil, the quaternary methiodide of which loses aniline and suffers demethylation on heating with hydrochloric acid (7); *o*-methoxybenzaldehyde (but not the *m*- or *p*-methoxy compound) behaves similarly, and so the —CHO and —OMe groups in cotarnine are considered to be *ortho* to each other. Cotarnine can accordingly be written as (XIII) and the anil as (XIV). This orientation of substituents was confirmed by the synthesis of cotarnic acid (XIX) as shown, (XV) → (XIX) (35).

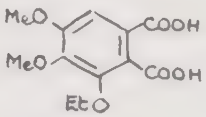
It was argued by Decker (4) that the —CHO and —NH— groups of (XIII) would not exist as such in close proximity, and he sug-



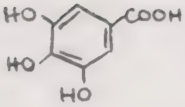
(IX)



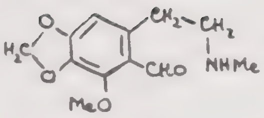
(X)



(XI)



(XII)



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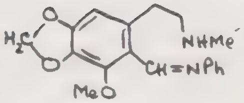
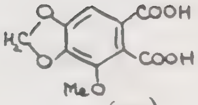
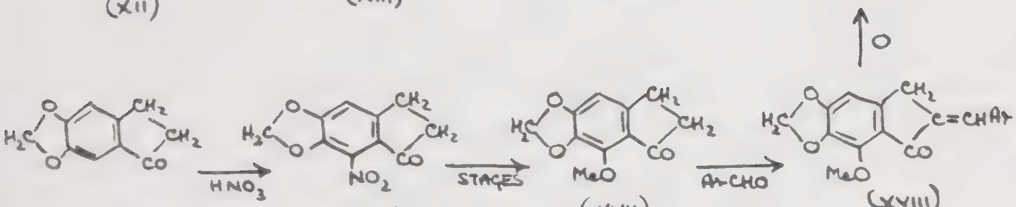


(XIV)



(XIX)



(XV) (XVI) (XVII) (XVIII)

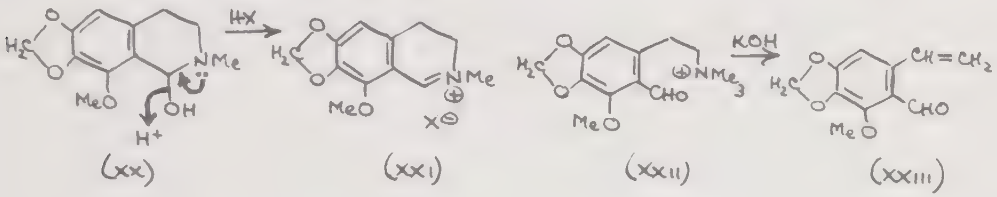
gested the carbinolamine structure (XX) for cotarnine, and indeed the ultraviolet spectrum of the alkaloid does not show the presence of any of the aldehydic form (XIII) in neutral solution. Cotarnine readily forms yellow salts of the general type (XXI) and in hydrolytic solvents the alkaloid exists largely as (XXI, X = OH).

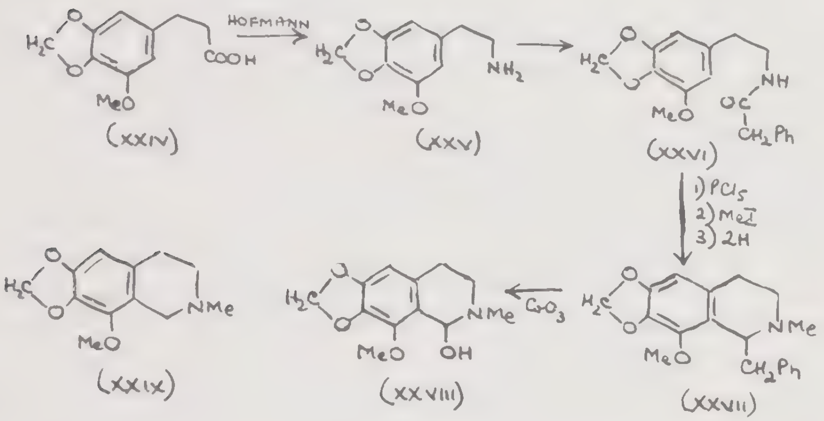
When cotarnine is treated with methyl iodide a mixture of cotarnine methiodide and cotarnine methine methiodide (XXII) is obtained, and the second of these salts is decomposed by alkalis (Hofmann degradation) to the nitrogen-free product cotarnone (XXXIII), which affords cotarnic acid (XIX) on oxidation (44).

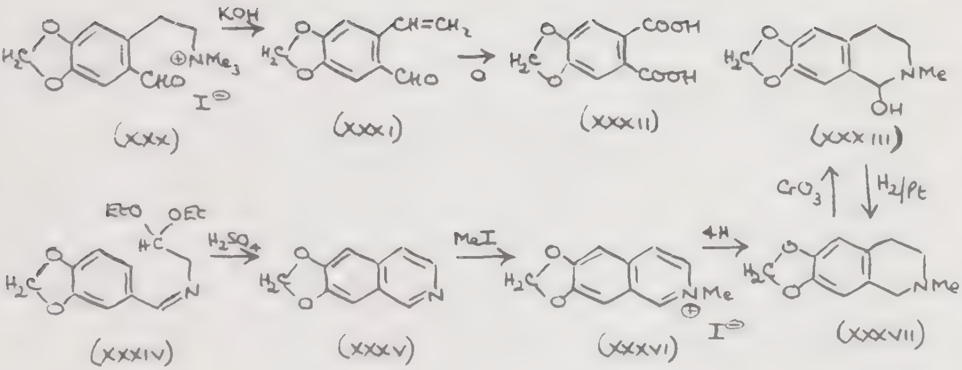
Cotarnine was synthesized by Salway (47) by the route shown in formulas (XXIV) and (XXVIII). Catalytic reduction of cotarnine yields hydrocotarnine (XXIX) (2), which is also obtainable by the hydrolysis of narcotine, and has been isolated from opium (15). This reduction involves the hydrogenolysis of the benzyl alcoholic hydroxyl group.

Hydrastinine, which is obtained by the oxidative hydrolysis of hydrastine (see below) bears a close relationship to cotarnine. It has the composition $C_{11}H_{13}O_3N$, and contains one methylenedioxy group and one —NMe— group. It may be converted through methylhydrastinine methiodide into the neutral hydrastal (XXXI), oxidation of which furnishes hydrastic acid which has been identified as 4,5-methylenedioxyphthalic acid (XXXII).

These results suggest that hydrastinine has the structure (XXXIII), i.e., desmethoxycotarnine, and this was confirmed by the synthesis of the base. Piperonal was condensed with amino-acetal giving the Schiff's base (XXXIV) which was converted into hydrohydrastinine (XXXVII) as shown (11); hydrohydrastinine had previously been oxidized to hydrastinine (10). Hydrohydrastinine, which is a hydrolysis product of hydrastine (10) and has been isolated from *Corydalis tuberosa* (55), may be prepared by the reduction of hydrastinine, and also by the reduction of hydrocotarnine (XXIX) with sodium and isoamyl alcohol (2,39), during which process a methoxyl group is eliminated. The mechanism of this reduction has been discussed by Clayson (2).


H₂C
NMe
MeO
OH
H⁺
(XX)
HX
H₂C
NMe
MeO
X⊖
(XXI)
H₂C
⊕NMe₃
CHO
MeO
(XXII)
KOH
H₂C
CH=CH₂
CHO
MeO
(XXIII)


H₂C
COOH
MeO
(XXIV)
HOFMANN
H₂C
NH₂
MeO
(XXV)
H₂C
NH
MeO
OC
CH₂Ph
(XXVI)
1) PCl₅
2) MeI
3) 2H
H₂C
NMe
MeO
CH₂Ph
(XXVII)
CrO₃
H₂C
NMe
MeO
OH
(XXVIII)
H₂C
NMe
MeO
(XXIX)


H₂C
⊕NMe₃
CHO
I⊖
(XXX)
KOH
H₂C
CH=CH₂
CHO
(XXXI)
O
H₂C
COOH
COOH
(XXXII)
H₂C
NMe
OH
(XXXIII)
CrO₃
H₂/Pt
EtO
OEt
HC
H₂C
N
(XXXIV)
H₂SO₄
H₂C
N
(XXXV)
MeI
H₂C
NMe
I⊖
(XXXVI)
4H
H₂C
NMe
(XXXVII)

2. THE BENZYLISOQUINOLINE ALKALOIDS

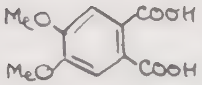
A. Papaverine (LIV).

Papaverine is one of the principal alkaloids of opium; it has the composition $C_{20}H_{21}O_4N$, is a tertiary base, and it contains four methoxyl groups. It also contains a —CH_2— group, which may be oxidized to —CO— by dichromate, the product being papaveraldine (12,19), which as the alkaloid xanthaline, has been isolated from opium. When papaverine is fused with potassium hydroxide two substances, $C_{11}H_{11}O_2N$ and $C_9H_{12}O_2$, are formed, and these two account for all the twenty carbon atoms of the alkaloid. The substance $C_{11}H_{11}O_2N$ is basic and on demethylation and distillation with zinc dust it is converted into isoquinoline; on oxidation it affords *m*-hemipinic acid (XXXVIII), which is distinguished from hemipinic acid (XXXIX) by the fact that it gives only one monoethyl ester and by the fact that on demethylation it furnishes a dihydroxy compound that forms only one monoethyl ether. The base $C_{11}H_{11}O_2N$ is thus seen to be 6,7-dimethoxyisoquinoline and this identity was confirmed by synthesis from veratric aldehyde and aminoacetal, (XL) → (XLI).

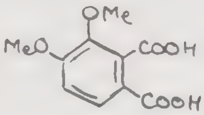
The compound $C_9H_{12}O_2$ is easily oxidized to veratric acid (XLII) by permanganate, and is thus 3,4-dimethoxytoluene (homoveratrole) (XLIII). The mode of linkage of these two units in papaverine is shown by the oxidation of the alkaloid to 6,7-dimethoxyisoquinoline-1-carboxylic acid (XLIV), in which the position of the hydroxyl group is shown by further oxidation to pyridine 1,2,3-tricarboxylic acid (XLV).

Papaverine is thus allotted the structure (LIV), which has been confirmed by various syntheses. As papaverine has considerable pharmacological value, and as it is present in opium to the extent of only 0.5–1%, practicable methods of synthesis of the base are of considerable importance. Two syntheses of the alkaloid may be given.

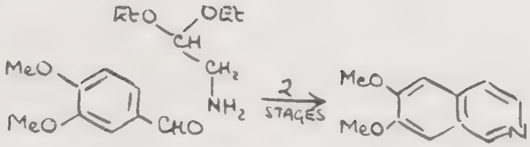
(*a*) the amide (LII), which may be prepared in a variety of ways,



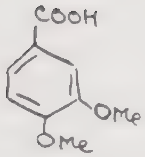
(XXXVIII)



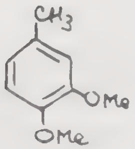
(XXXIX)



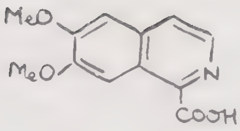
(XL) (XLI)



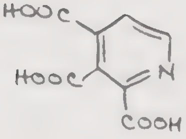
(XLII)



(XLIII)



(XLIV)



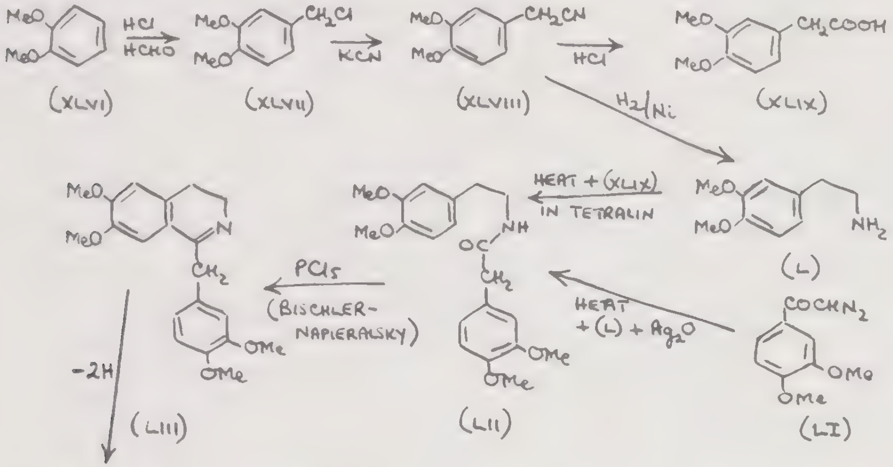
(XLV)

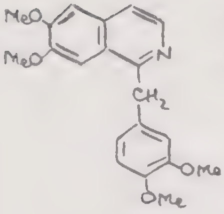
e.g., (XLVI) ⟶ (XLIX) + (L) ⟶ (LII), when subjected to Bischler-Napieralsky isoquinoline ring closure affords 3,4-dihydropapaverine (LIII), which is easily dehydrogenated to papaverine (LIV) (36,54,20).

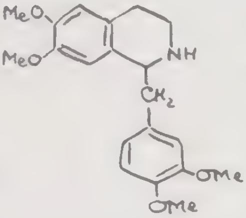
(*b*) The use of the somewhat more accessible veratric acid in place of homoveratric acid is made possible by an application of the Arndt-Eistert reaction for the synthesis of the amide (LII). The diazoketone (LI), prepared by the interaction of diazomethane and veratroyl chloride, reacts with homoveratrylamine in the presence of silver oxide to give the amide (LII) (6).

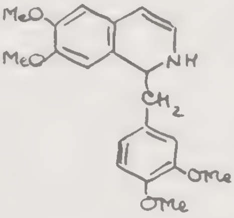
The reduction of papaverine with tin and hydrochloric acid affords two bases, viz., 1,2,3,4-tetrahydropapaverine (LV) (38), which can be dehydrogenated to papaverine (54), and pavine. Pavine is a secondary amine of composition $C_{20}H_{23}O_4N$, i.e., it is a dihydropapaverine. The base may be resolved into optical isomers (37). It cannot be further reduced, nor can it be oxidized to papaverine, and therefore it cannot be 1,2-dihydropapaverine (LVI). The structure (LVII) was advanced for this base by Pyman, but against this may be cited the fact that no veratric acid has ever been isolated from the products of oxidation of pavine.

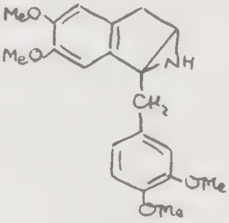
When *N*-methyl-1,2-dihydropapaverine (LVI, NH = NMe) is demethylated with boiling hydrobromic acid the double bond disappears and *N*-methylnorpavine is formed; this substance can be methylated to *N*-methylpavine. The disappearance of the double bond must result from the addition to the unsaturated linkage of some other part of the molecule, and this led Schöpf (48) to suggest the structure (LIX, R = H) or (LVIII) for pavine. Of these the structure (LIX, R = H) was shown to be correct by the degradation of *N*-methylpavine (LIX, R = Me) as shown in the formulas (LIX, R = Me) ⟶ (LXII), the structure of the final dibasic acid (LXII) being confirmed by synthesis (1). The ketone (LXIII) would have been the end-product of this series of degradations if pavine had the structure (LIX).

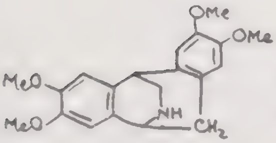


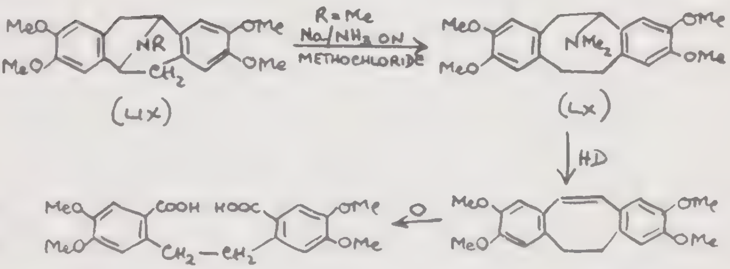

(LIV)

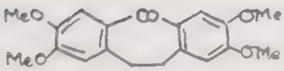

(LV)


(LVI)


(LVII)


(LVIII)




(LXIII)

B. Laudanosine (LXV).

This alkaloid, one of the minor bases obtained from opium, has the composition $C_{21}H_{27}O_4N$ and contains four —OMe groups and one —NMe— group. It is obtained in the (±) form by the reduction of the *N*-methylquaternary salts of papaverine (LXIV) and has the constitution (LXV). Laudanosine may be synthesized from the same intermediate, the amide (LII), as is used in the synthesis of papaverine. Cyclization of the amide affords dihydropapaverine (LIII) as before, and reduction of the methochloride or methiodide of this yields (±)-laudanosine (36). Exhaustive methylation of laudanosine leads successively to the base (LXVI) and the nitrogen-free product (LXVII).

Laudanosine, on demethylation, affords the tetrahydroxy compound laudanosoline, and, in an attempt to simulate the biosynthesis of the aporphine alkaloids (see Chapters 4 and 11), Robinson attempted to convert this into norglaucine (LXVIII) by oxidation, but the only material that could be isolated from this reaction was the tetrahydropyrrocolinium salt (LXIX) (42).

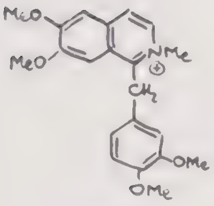
Cyclization of the nitrogen atom with the reactive position of the veratryl system with the introduction of a bridge carbon atom occurs when tetrahydropapaverine (LVI) is heated with formaldehyde, the product being the base (LXX) which has the skeleton of the alkaloids of the protoberberine group and is actually identical with (±)-coreximine dimethyl ether (3).

3. THE PHTHALIDEISOQUINOLINE ALKALOIDS

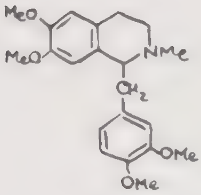
The alkaloids of this group are structurally similar in many respects to laudanosine, but they are biogenetically much more closely related to the alkaloids of the protoberberine group, from which they are believed to arise by oxidation.

A. Narcotine (LXXIV).

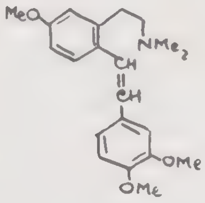
This base, one of the major alkaloids of opium, has the composition $C_{22}H_{23}O_7N$ and contains three methoxyl groups, one methylenedioxy group, and one —NMe— group. The remaining two oxygen atoms are present in a lactone system. The alkaloid is readily



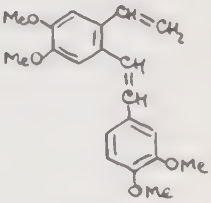
(LXIV)



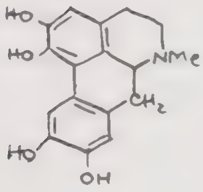
(LXV)



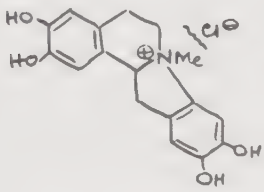
(LXVI)



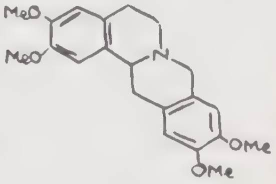
(LXVII)



(LXVIII)



(LXIX)



(LXX)

cleaved into two fragments which together account for all the carbon, oxygen, and nitrogen atoms in the original molecule, and indeed all the phthalideisoquinoline alkaloids may be so decomposed, making the elucidation of their structures now a relatively simple matter.

Narcotine may be split in three ways (34):

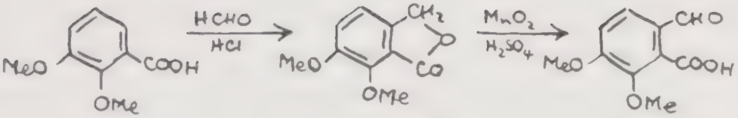
(*a*) Oxidative hydrolysis with dilute sulfuric acid to cotarnine (XX) and opianic acid.

(*b*) Hydrolysis with water to hydrocotarnine (XXIX) and opianic acid.

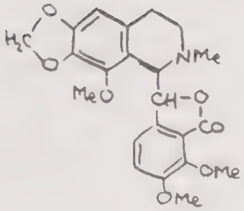
(*c*) Reductive hydrolysis with zinc and sulfuric acid to hydrocotarnine and meconine.

Of these fragments cotarnine and hydrocotarnine have already been discussed. **Opianic acid,** $C_{10}H_{10}O_5$, is a monobasic acid containing two methoxyl groups one —CHO group and one —COOH group. On oxidation it is converted into hemipinic acid (XXXIX) (65) and on reduction it yields the lactone meconine. That **meconine** has the structure (LXXII) is amply proved by its synthesis from 2,3-dimethoxybenzoic acid, (LXXI) → (LXXII) (5). This process may also be used as part of a synthesis of opianic acid since the latter is obtained in almost quantitative yield by the oxidation of meconine with manganese dioxide and sulfuric acid (46); opianic acid is thus allotted the structure (LXXIII).

When these fragments are put together the formula (LXXIV) emerges for narcotine. The alkaloid was synthesized by Perkin and Robinson (34) by the condensation of cotarnine (XX) and meconine (LXXII); the product was gnoscopine (racemic narcotine), which on resolution yielded (–)-narcotine identical with the natural base. Nitro and monohalogenated meconines condense with cotarnine more readily than does the unsubstituted lactone, giving the corresponding gnoscopines, but the base from nitromeconine belongs to a series stereoisomeric with that obtained from iodomeconine or meconine itself; the center of the isomerism is presumably the asymmetric carbon atom of the phthalide unit (16). Both series of gnoscopines may be degraded to the same narceine (see the following section).



(LXXI) (LXXII) (LXXIII)



(LXXIV)

B. Hydrastine (LXXV).

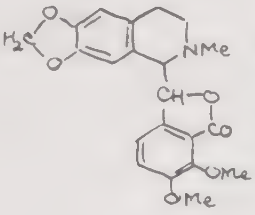
This base, $C_{21}H_{21}O_6N$, from *Hydrastis canadensis* L., contains one methylenedioxy group, two methoxyl groups, and one —NMe— group. It may be cleaved by oxidative hydrolysis to opianic acid and hydrastinine (XXXIII) (9). From the known structure of hydrastinine the structure of hydrastine is seen to be (LXXV), and this has been confirmed by synthesis. The first synthesis achieved was parallel to the synthesis of narcotine and involved the condensation of hydrastinine with nitromeconine, followed by reduction of the resulting nitro compounds and subsequent deamination. This process afforded two racemates, (±)-hydrastine-*a* and (±)-hydrastine-*b*, and of these the *a*-isomer was resolved giving (–)-hydrastine-*a* identical with the natural base (13,17,29). Subsequently a synthesis of the alkaloid was achieved by the dehydration of the amide (LXXVI) to the base (LXXVII), followed by reduction (13).

Hydrastine may be reduced by lithium aluminum hydride to the diol (LXXVIII) and this on treatment with thionyl chloride is converted into a quaternary salt with simultaneous dehydration, the product being dihydroanhydroberberinium methochloride (LXXIX), which on heating affords dihydroanhydroberberine (LXXX) with loss of methyl chloride (33). This is of interest in view of the isolation of both hydrastine and berberine from the same plants.

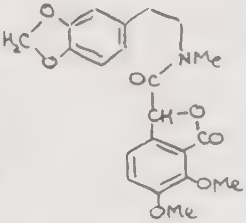
C. Narceine (LXXXIV).

Although this base is not an isoquinoline it is a degradation product of narcotine and occurs naturally in opium. When narcotine methochloride is decomposed by steam in the presence of alkali narceine is obtained. It is presumably the result of Hofmann degradation, leading to the unsaturated lactone (LXXXII), which on hydrolysis and ketonization affords narceine (LXXXIV).

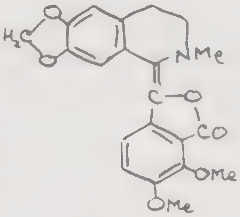
The structure (LXXXIV) is confirmed in the following way. Narceine forms a phenylhydrazone and an isonitroso compound (8). The



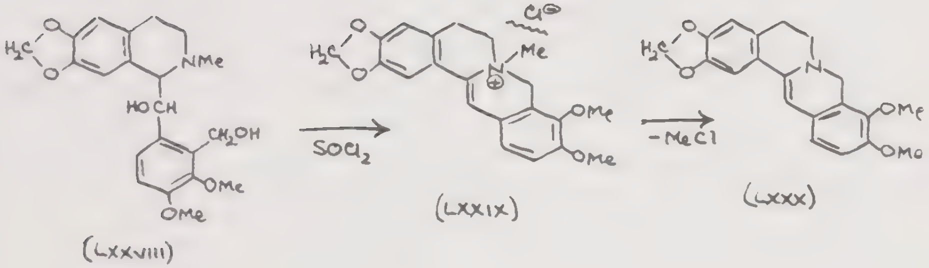
(LXXV)



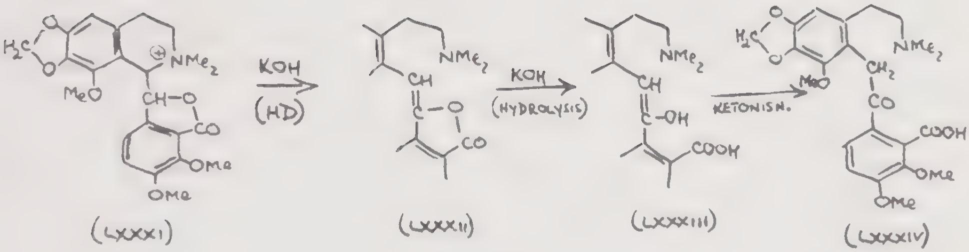
(LXXVI)



(LXXVII)



(LXXVIII) (LXXIX) (LXXX)



(LXXXI) (LXXXII) (LXXXIII) (LXXXIV)

latter when heated is split into hemipinic acid and a base (LXXXVI) that affords cotarnonitrile (LXXXVII) when subjected to Hofmann degradation. Cotarnonitrile is also obtained when the oxime of *N*-methylcotarnine methochloride (LXXXVIII) is heated with alkali, and must have the structure (LXXXVII) (45). Isonitrosonarceine must therefore have the constitution (LXXXV).

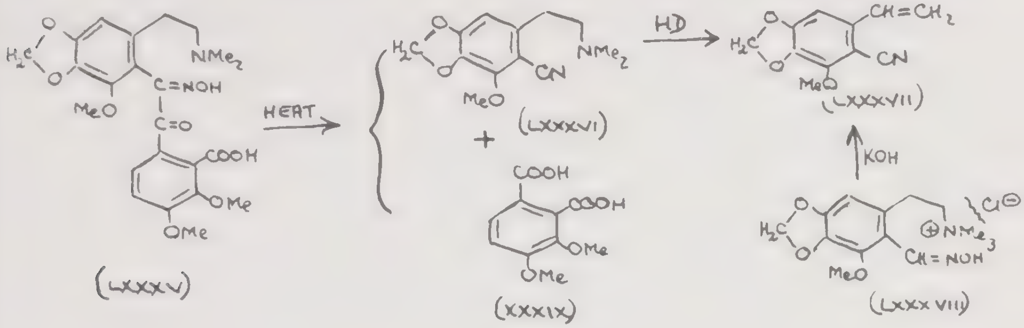
For a more detailed treatment of the phthalideisoquinoline alkaloids see refs. 14 and 59.

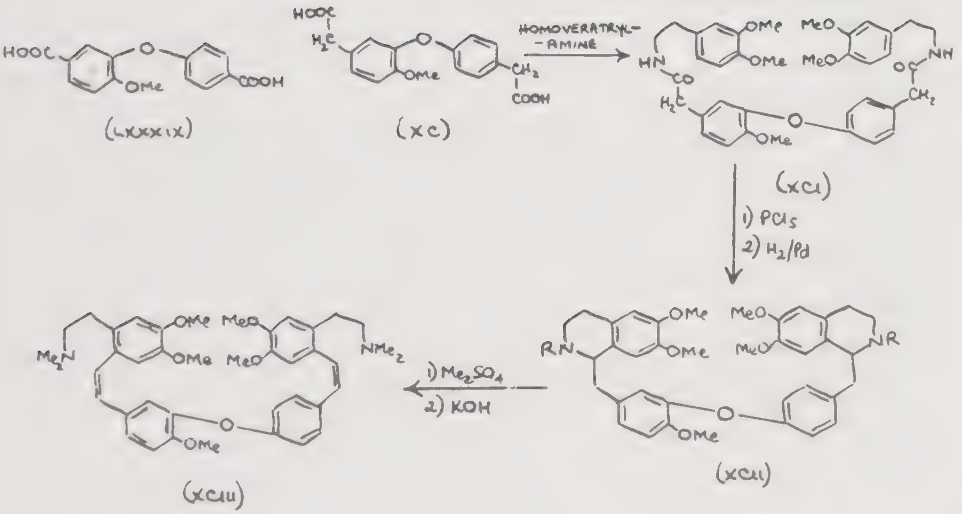
4. THE BISBENZYLISOQUINOLINE ALKALOIDS

A group of alkaloids occurs in Nature formed by the linkage of two molecules of a simple benzylisoquinoline alkaloid, the junction being an ether linkage between two aromatic nuclei. The group may be subdivided into three, and one representative of each subgroup will be considered here. Several methods of degradation have been applied to the study of these alkaloids, the most important being the fission of the molecule into two fragments by oxidation, before or especially after Hofmann degradation. Fission at the diphenyl ether linkage only, by sodium and liquid ammonia, to give two simple benzylisoquinolines has recently been developed.

A. Alkaloids Containing One Diphenyl Ether Linkage (XCII).

Dauricine, found in *Menispermum dauricum* DC. (22) and *Menispermum canadense* L. (31), has the composition $C_{38}H_{44}O_6N_2$ (25) and contains one phenolic hydroxyl group, four methoxyl groups, and two —NMe— groups. Methylation of the —OH and —NMe— groups, followed by Hofmann degradation affords a methine base, further degradation of which yields trimethylamine and a nitrogen-free product. This nitrogen-free product on oxidation gives *m*-hemipinic acid (XXXVIII) and 4′,5-dicarboxy-2-methoxydiphenyl ether (LXXXIX) (23,24). The methine base (XCIII) has been synthesized by the route shown, (XC) → (XCII, R = H) → (XCIII), showing that dauricine methyl ether is (XCII, R = Me) (25). For the position of the hydroxyl group in dauricine, see the following section under "oxyacanthine."


HEAT
HD
KOH
(LXXXV)
(LXXXVI)
(XXXIX)
(LXXXVII)
(LXXXVIII)


HOMOVERATRYL-AMINE
1) PCl5
2) H2/Pd
1) Me2SO4
2) KOH
(LXXXIX)
(XC)
(XCI)
(XCII)
(XCIII)

B. Alkaloids Containing Two Diphenyl Ether Linkages (XCIX).

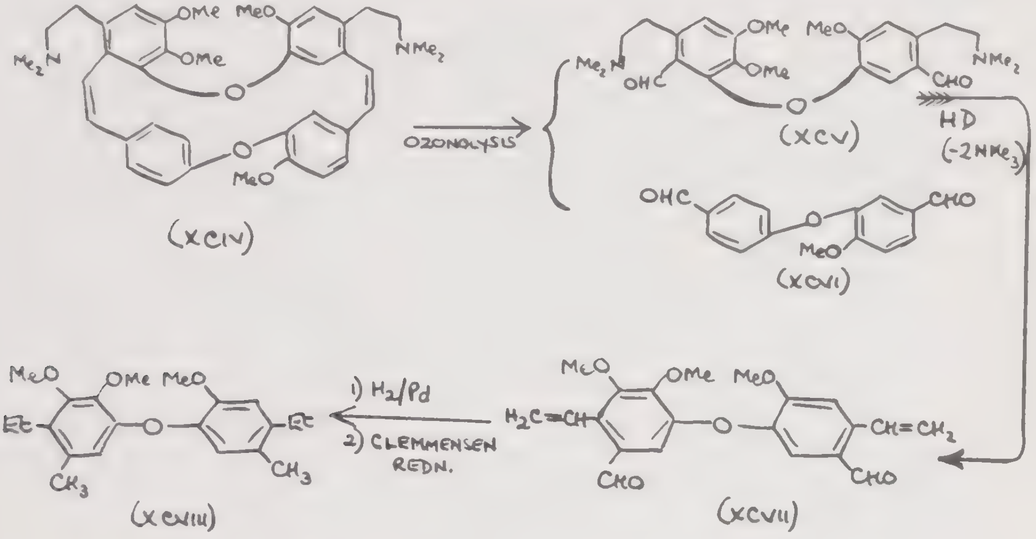
Oxyacanthine, obtained from the roots of several *Berberis* species, has the composition $C_{37}H_{40}O_6N_2$ (56) and contains one phenolic hydroxyl group, three methoxyl groups, and two —NMe— groups. Hofmann degradation of the methyl ether gives a methine base (XCIV) which on oxidation affords the acid (LXXXIX); the alkaloid ethyl ether similarly affords the ethoxy analog of (LXXXIX), showing that the phenolic hydroxyl group in oxyacanthine is *ortho* to the ether linkage (58,63). (In a similar way the phenolic hydroxyl group of dauricine was shown to occupy the same position.)

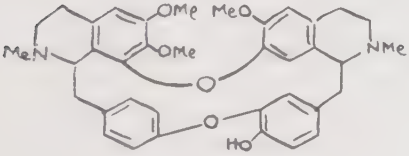
The methine base (XCIV) on ozonolysis yields the aldehydes (XCV) and (XCVI); of these (XCV) on exhaustive methylation affords the nitrogen-free product (XCVII) which, when subjected to reduction, catalytically and by Clemmensen's method yielded (XCVIII), identical with a synthetic specimen (62,64). These results indicate the structure (XCIX) or (C) for oxyacanthine, but as (C) has been proved, by sodium/ammonia fission of the methyl ether as shown by the dotted lines (61), to be the alkaloid berbamine, oxyacanthine must be (XCIX).

C. Alkaloids Containing Three Diphenyl Ether Linkages (CI).

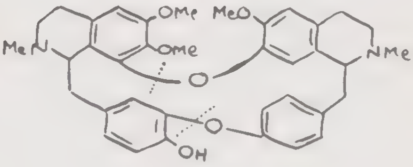
Trilobine, which occurs in *Cocculus trilobus* DC. (21), has the composition $C_{36}H_{36}O_5N_2$ and contains two methoxyl groups and two —NMe— groups. Hofmann degradation furnishes a methine base, oxidation of which yields the dibasic acid (LXXXIX) already obtained from dauricine and oxyacanthine (26). Ozonolysis of the methine affords the dialdehydes (XCIV), identified by oxidation to the acid (LXXXIX) and (CIII) (27). The structure of the second of these aldehydes (CIII) was elucidated by Hofmann degradation to (CIV), followed by hydrogenation to (CV) and Clemmensen reduction to (CVI), which was identified with material prepared by synthesis (60). From these results the methine must have the structure (CII) and trilobine (CI).

A detailed account of the bisbenzylisoquinoline alkaloids is given by Kulka (28).

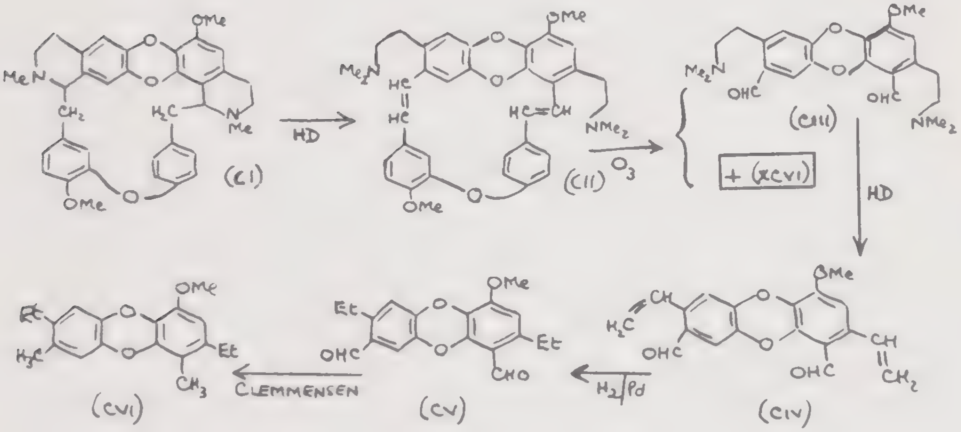

(XCIV)
OZONOLYSIS
(XCV)
HD
(-2NMe₃)
(XCVI)
(XCVII)
1) H₂/Pd
2) CLEMMENSEN REDN.
(XCVIII)



(XCIX)

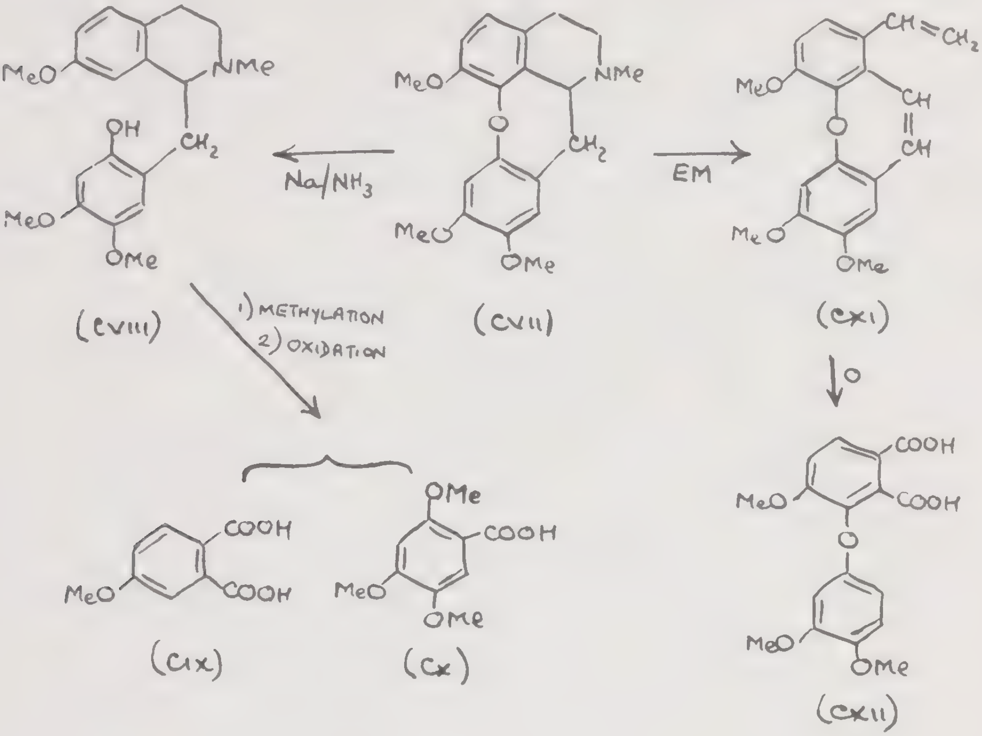


(C)


(CI)
HD
(CII)
O₃
(CIII)
+ (XCVI)
HD
(CIV)
H₂/Pd
(CV)
CLEMMENSEN
(CVI)

5. CULARINE (CVII)

This base, which is a major alkaloid of *Corydalis claviculata* (30), is of interest as it contains a diphenyl ether linkage inside the molecule of a simple benzylisoquinoline alkaloid. It has the composition $C_{20}H_{23}O_4N$ and contains three methoxyl groups and one —NMe— group. When subjected to exhaustive methylation (two stages) it gives a nitrogen-free product, $C_{19}H_{18}O_4$, which may be oxidized to a tribasic acid $C_{18}H_{16}O_{10}$. Sodium/ammonia fission of the diphenyl ether system affords a phenolic base, which on methylation and oxidation is converted into the acids (CIX) and (CX). These reactions show that cularine must have the structure (CVII). Alternative positions for the ether bridge are rejected on steric grounds (32). The nitrogen-free product is (CXI) and the tribasic acid (CXII).


MeO
NMe
OH
CH2
MeO
OMe
(CVIII)
Na/NH3
MeO
NMe
O
CH2
MeO
OMe
(CVII)
EM
CH=CH2
MeO
CH
CH
O
MeO
OMe
(CXI)
O
1) METHYLATION
2) OXIDATION
COOH
MeO
COOH
(CIX)
OMe
COOH
MeO
OMe
(CX)
COOH
MeO
COOH
O
MeO
OMe
(CXII)

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CHAPTER 4

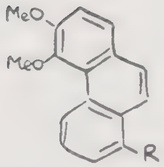
ALKALOIDS OF THE ISOQUINOLINE GROUP: II

1. THE APORPHINE ALKALOIDS

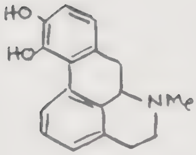
The alkaloids of the aporphine group are widely distributed. The simplest are apomorphine and morphothebaine; these bases do not occur naturally, but are obtained by acid rearrangement of morphine and thebaine, respectively; the methods used for the elucidation of their structures and for their synthesis are, however, generally applicable to the naturally occurring alkaloids of this group, and they can with profit be considered at this point.

A. Apomorphine (II).

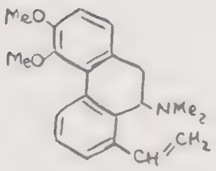
This is formed when morphine is heated with concentrated hydrochloric acid at 140–150° (16); it has the composition $C_{17}H_{17}O_2N$ and contains two phenolic hydroxyl groups and one —NMe— group. The dimethyl ether suffers degradation by Hofmann's method giving a mixture of two methine bases. The nitrogen-free product of exhaustive methylation is 3,4-dimethoxy-8-vinylphenanthrene (I, R = $CH=CH_2$) which can be converted through the acid (I, R = COOH) and subsequently through (I, R = $CONH_2$), (I, R = NH_2), and (I, R = OH) into 3,4,8-trimethoxyphenanthrene (I, R = OMe) (22,24). As apomorphine behaves as a derivative of catechol the —OMe group appearing at position 8 in (I, R = OMe) must indicate the point of attachment of the side chain. Of the two methine bases obtained in the first stage of exhaustive methylation, one is optically active and one inactive, showing that the nitrogen atom must be attached to position 9 (or, very improbably, position 10) of the phenanthrene system; thus apomorphine is (II) and the bases from the Hofmann degradation of the dimethyl ether are (III) and (IV);



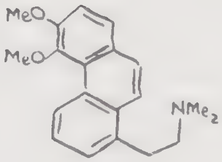
(I)



(II)



(III)



(IV)

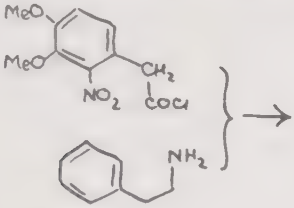
both these bases give the vinyl compound (I, R = CH ═ CH_2) on further degradation. The structure (II) for apomorphine was confirmed by the total synthesis of the dimethyl ether by the route shown, (V) ⟶ (IX) (26).

B. Morphothebaine (X).

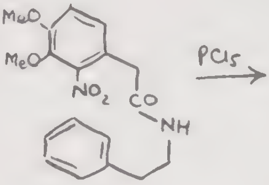
This is obtained when thebaine is heated with concentrated hydrochloric acid at 100° (14); it has the composition $C_{18}H_{19}O_3N$ and has the structure (X). It may be degraded in like manner to apomorphine to 3,4,6,8-tetramethoxyphenanthrene (23); decarboxylation of the intermediate trimethoxyphenanthrene-8-carboxylic acid affords 3,4,6-trimethoxyphenanthrene. Morphothebaine dimethyl ether has been synthesized by a route analogous to that used for the synthesis of apomorphine dimethyl ether, starting from *m*-methoxyphenylethylamine (11).

For a detailed account of these two bases, see the author's monograph on the morphine alkaloids (5); for the mechanism of the production of the bases from morphine and thebaine see Chapter 5.

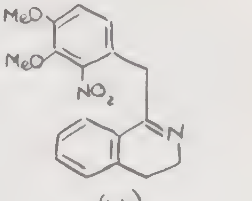
A wide variety of aporphine alkaloids occur in nature, e.g., glaucine (XII), which may be prepared from aminolaudanosine (XI) by the Pschorr phenanthrene cyclization process (8), and corytuberine (XIII). Trioxy- and dioxyaporphines are also known, and all aporphines, the structures of which have been determined, have two oxygen functions in positions 5 and 6 (see XII). The structures of most aporphines have been determined by degradation to phenanthrene carboxylic acids followed by decarboxylation of these to phenanthrene derivatives. The identification of these final products, however, does not allow an unambiguous allocation of the position of the substituents in the parent alkaloid, since two alkaloids, isomeric and having the positions of the substituents in the two aromatic nuclei reversed, would give the same phenanthrene derivative on degradation in this way. It is only by synthesis of the alkaloid, or by degradation to an ethyl phenanthrene followed by synthesis that the position of the substituents can be determined with certainty in many cases.



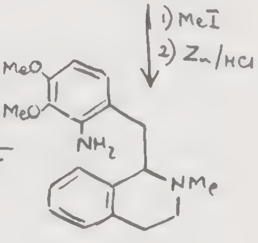
(v)



(vi)



(vii)



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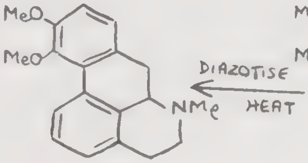

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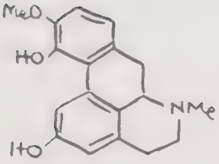

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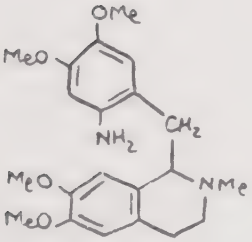

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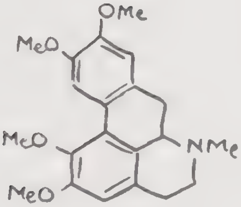

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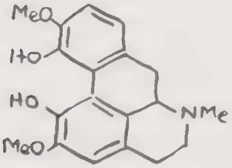


(xiii)

2. THE PROTOBERBERINE ALKALOIDS

These bases can be regarded as benzylisoquinoline alkaloids in which a fourth ring has been created by the addition of a bridge carbon atom. They are widely distributed in Nature.

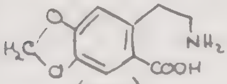
A. Berberine (XXII).

This alkaloid occurs in a considerable number of *Berberis* species. It has the composition $C_{20}H_{18}O_5N$ and contains one methylenedioxy group, two methoxyl groups, and one hydroxyl group. It can be reduced to tetrahydroberberine, $C_{20}H_{20}O_4N$. The principal information of structural significance comes from the oxidation with alkaline permanganate, when berberine yields oxyberberine, berberilic acid, and berberal, all of which retain the twenty carbon atoms of the alkaloid (18).

Berberilic acid, $C_{20}H_{19}O_9N$, contains two carboxyl groups and is readily converted into anhydroberberilic acid, $C_{20}H_{17}O_8N$, which contains one carboxyl group. Hydrolysis with sulfuric acid converts it into hemipinic acid (XV) and the acid (XIV), and berberilic acid must therefore have the structure (XVI) (21).

Berberal, $C_{20}H_{17}O_7N$, is hydrolyzed by sulfuric acid to noroxyhydrastinine (XVII) and ψ-opianic acid (XVIII), which closely resembles opianic acid (LXXIII in Chapter 3). ψ-Opianic acid may be reduced to ψ-meconine and may be oxidized to hemipinic acid; as the structure of opianic acid has already been determined (Chapter 3) it must accordingly have the structure (XVIII) and ψ-meconine must be (XIX). These results suggest the structure (XXI) for berberal, but (XX) is regarded as more likely (21) in view of the fact that opianic acid, on reaction with aniline, becomes attached to the nitrogen atom through the carbon atom of the aldehydic group (15).

As berberal (XX) arises from berberine by oxidation, the carbon skeleton of the alkaloid must be that of (XXIII). Berberine when liberated from the sulfate by barium hydroxide exists as a strongly basic hydroxide (XXII) (7), and this has the same ultraviolet spectrum as the salts; however, when excess of alkali is added to the solution the sparingly soluble pseudo base (XXIII) is obtained. The ultraviolet spectrum of this shows many similarities with those of the pseudo base forms of cotarnine and hydrastinine.



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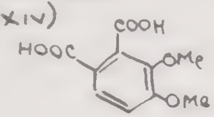

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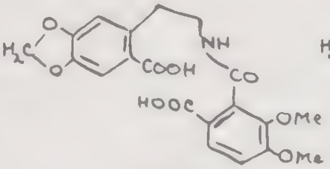

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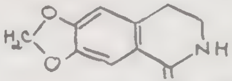

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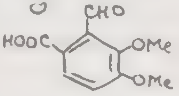

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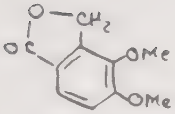

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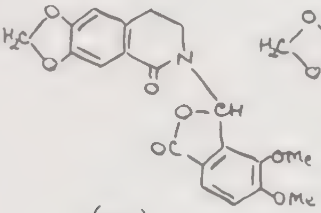

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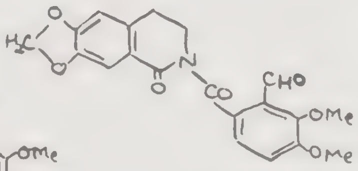
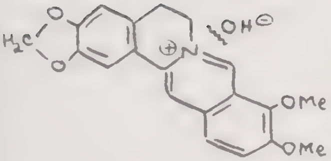
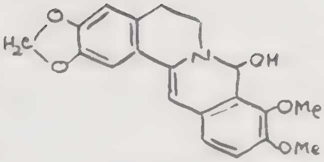


(XXI)



(XXII)



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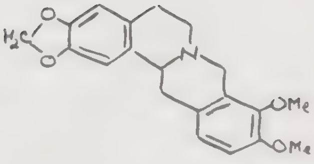

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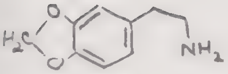

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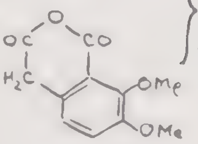

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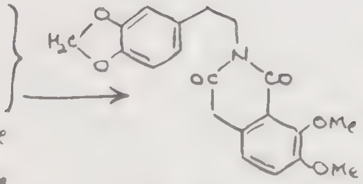

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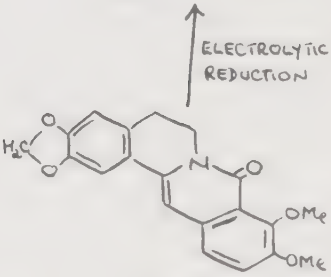


(XXVII)

Oxyberberine, the carbonyl compound (XXVII), has been synthesized by the route (XXV) ⟶ (XXVII) (13), and as it has been reduced to tetrahydroberberine, which has been oxidized to berberine, this constitutes a total synthesis of the alkaloid.

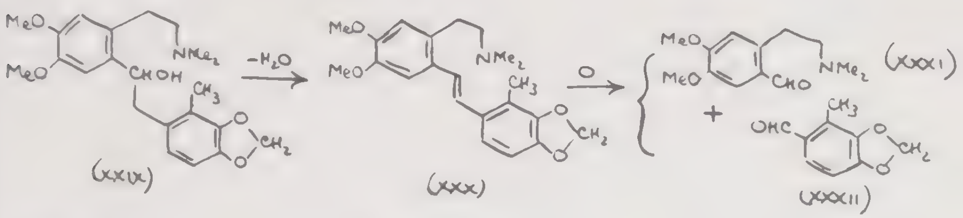
3. THE PROTOPINE ALKALOIDS

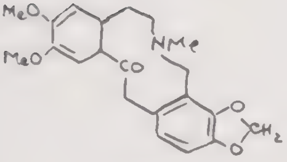
The alkaloids of this group are very closely related to those of the berberine group, from which they are very probably derived.

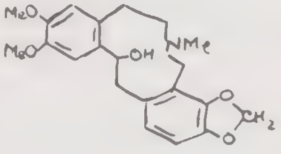
A. Cryptopine (XXXIII).

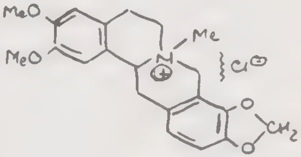
This is one of the minor alkaloids of opium; it has the composition $C_{21}H_{23}O_5N$, and contains one methylenedioxy group, two methoxyl groups, one —NMe— group, and one carbonyl group. Cryptopine methosulfate on reduction with sodium amalgam suffers Emde degradation and reduction of the carbonyl group giving tetrahydromethylcryptopine (XXIX), which may be dehydrated to anhydrotetrahydromethylcryptopine (XXX) and this on oxidation furnishes the aldehydes (XXXI) and (XXXII). The position of the hydroxyl group in (XXXIX) and therefore of the carbonyl group in cryptopine may be inferred as follows. Cryptopine (XXXIII) on reduction with sodium amalgam affords dihydrocryptopine (XXXIV), which with acetyl chloride affords two stereoisomeric quaternary chlorides of structure (XXXV) and differing only at the junction of the two saturated rings. These two salts closely resemble tetrahydroberberine (XXVIII) methochloride in all their reactions, and therefore have similar structures. The position of the carbonyl group in cryptopine is further indicated by the results of Hofmann degradation of cryptopine methosulfate, the products being γ-methylcryptopine (XXXVI) and β-methylcryptopine (XXXVII), the latter being formed from the initially produced alcohol (XXXVIII). γ-Methylcryptopine is the simplest derivative of cryptopine to show recognizable ketonic properties (19,20).

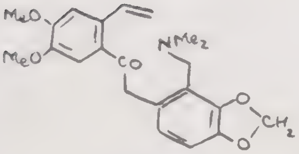
Cryptopine was finally synthesized as shown, (XXXIX) ⟶ (XLV) (12).

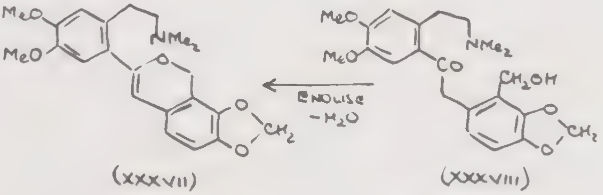


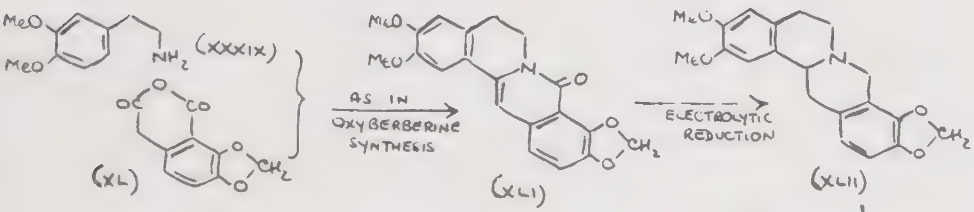

(XXXIII)

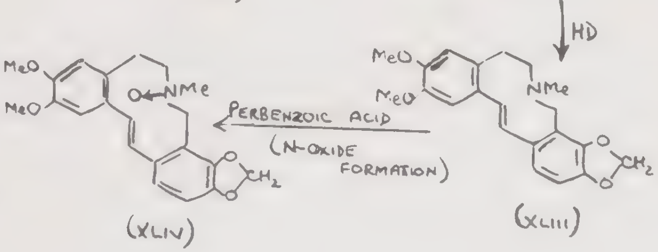

(XXXIV)

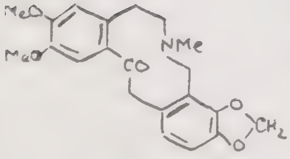

(XXXV)


(XXXVI)

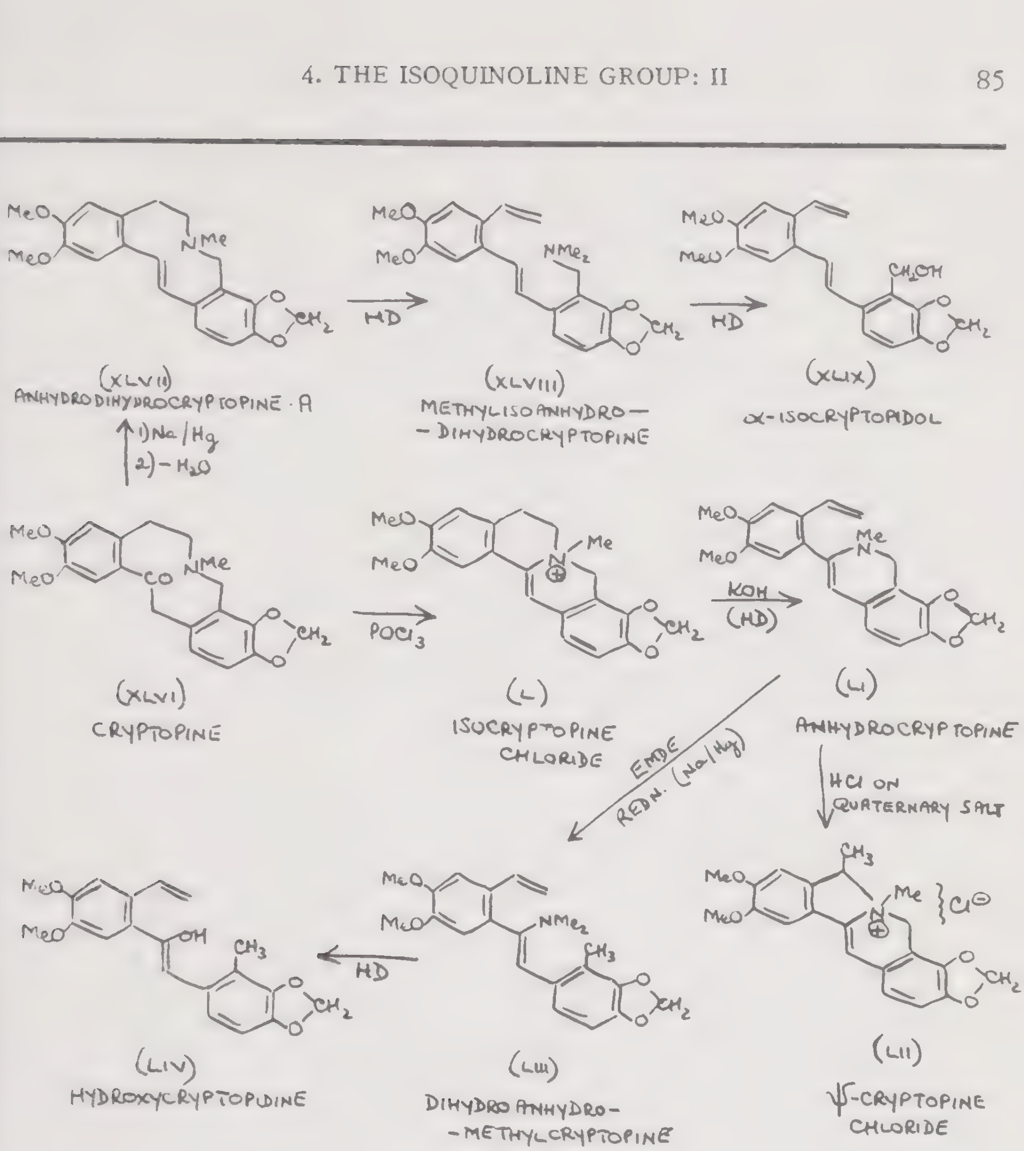







(XLV)

Several other degradations of cryptopine are shown in formulas (XLVI) → (LIV) (19,20).


MeO
MeO
NMe
O
CH2
(XLVII)
ANHYDRODIHYDROCRYPTOPINE · A
HD
NMe2
(XLVIII)
METHYLISOANHYDRO-
-DIHYDROCRYPTOPINE
HD
CH2OH
(XLIX)
α-ISOCRYPTOPIDOL
1) Na/Hg
2) −H2O
CO
(XLVI)
CRYPTOPINE
POCl3
Me
(L)
ISOCRYPTOPINE
CHLORIDE
KOH
(HD)
(LI)
ANHYDROCRYPTOPINE
EMDE
REDN. (Na/Hg)
HCl ON
QUATERNARY SALT
CH3
Cl⊖
(LII)
ψ-CRYPTOPINE
CHLORIDE
OH
HD
(LIV)
HYDROXYCRYPTOPIDINE
(LIII)
DIHYDRO ANHYDRO-
-METHYLCRYPTOPINE

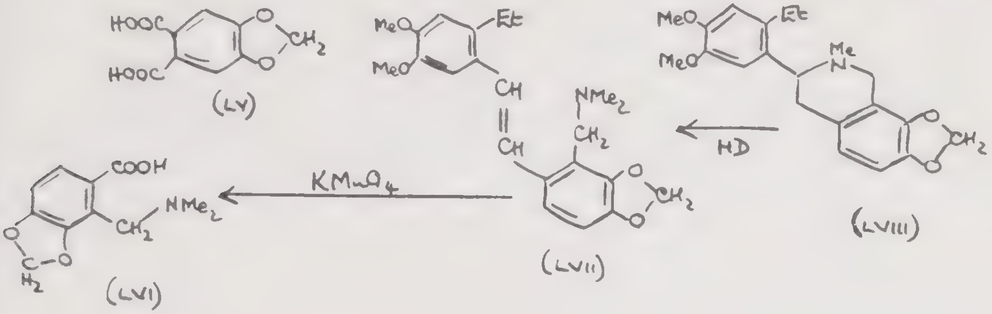
4. THE α-NAPHTHAPHENANTHRIDINE ALKALOIDS

A. Chelidonine (LXII) and Sanguinarine (LXI).

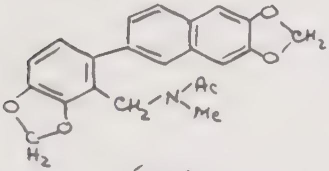
These two alkaloids, isolated from *Chelidonium majus* L. (9,25), are closely related. They have the compositions $C_{20}H_{19}O_5N$ and $C_{20}H_{14}O_5N$, respectively. Both contain two methylenedioxy groups. Chelidonine forms an optically active *O*-acetyl derivative on treatment with acetic anhydride at moderate temperatures, but at 140° dehydration occurs and an optically inactive *N*-acetyl compound results. Oxidation of the *O*-acetyl derivative with mercuric acetate followed by dehydration gives dihydrosanguinarine, which may be oxidized to sanguinarine by air (10).

Hofmann degradation of chelidonine affords a methine which is oxidized by permanganate to hydrastic acid (LV), and the acid (LVI) which may be synthesized from anhydrocryptopine (LI) via the bases (LVIII) and (LVII) (29).

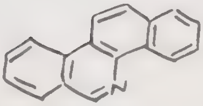
Oxidation of the optically inactive *N*-acetylanhydrochelidonine with nitric acid affords benzene-1,2,4-tricarboxylic acid, showing that a trisubstituted benzene ring must be interpolated between the two substituted aromatic nuclei, and the structure (LIX) for the *N*-acetyl compound meets all the requirements (27). Distillation of sanguinarine with zinc dust yields α-naphthaphenanthridine (LX), thus indicating the nature of the basic ring system (27). Sanguinarine may accordingly be formulated as (LXI). Chelidonine is allotted the structure (LXII), though the exact position of the hydroxyl group has not yet been determined; it is placed as shown to explain facile formation of an ether bridge on degradation of the dihydromethine (LXIII), the product of which, formulated as (LXIV), contains only inactive ether oxygen atoms (27).



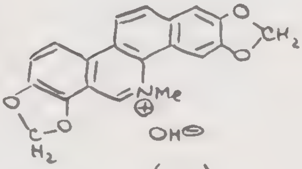
(LV) (LVI) (LVII) (LVIII)



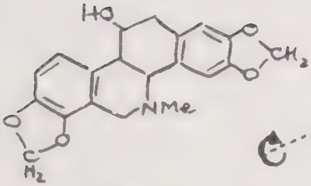
(LIX)



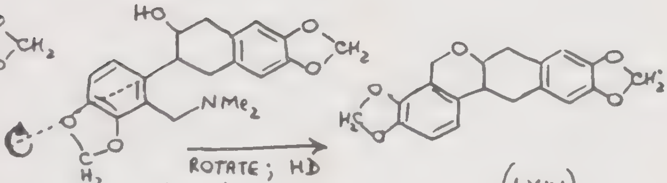
(LX)



(LXI)



(LXII)



(LXIII) (LXIV)

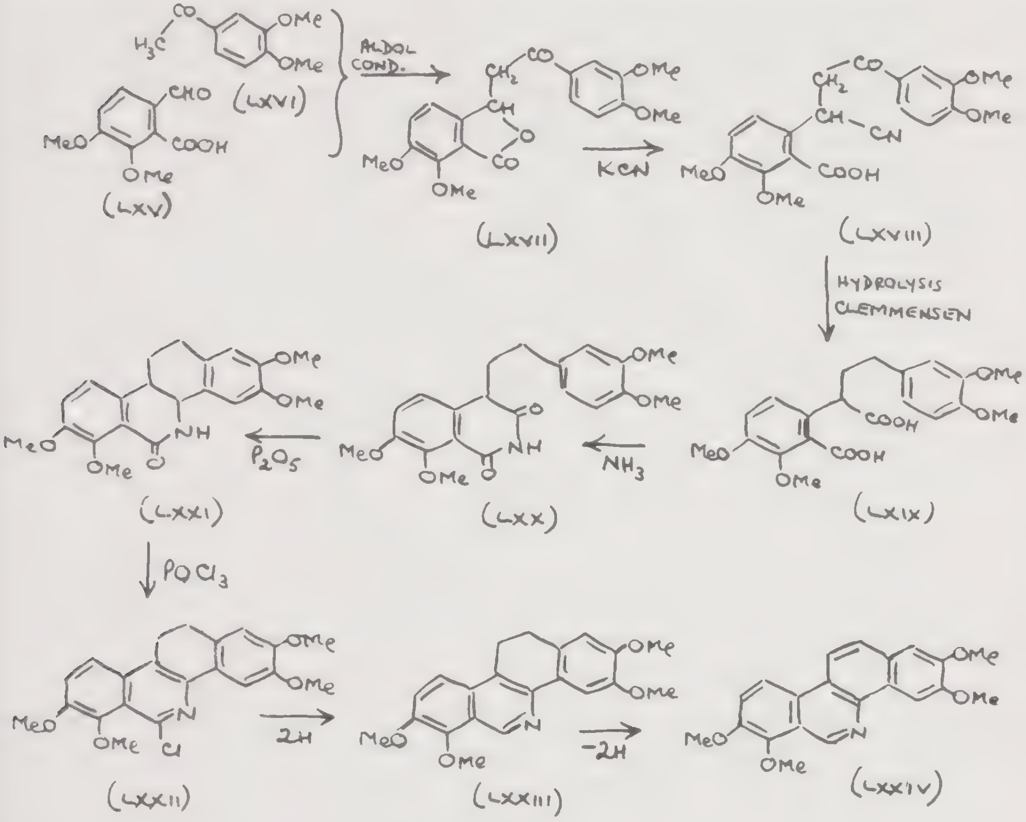
None of the alkaloids of this group has been synthesized, but the tetramethoxy compound (LXXIV), analogous to sanguinarine, has been prepared by the route (LXV) → (LXXIV) (1).

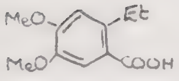
5. THE IPECACUANHA ALKALOIDS

A. Emetine (XCII).

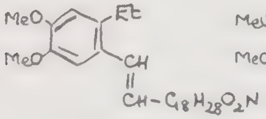
This base, which is one of the principal alkaloids of Ipecac roots, has the composition $C_{29}H_{40}O_4N_2$ and contains four methoxyl groups, one basic —NH— group, and one basic tertiary nitrogen. Complete methylation to *N*-methylemetine dimethiodide followed by Hofmann degradation affords methylemetine methine, degradation occurring at both nitrogen centers with the production of two double bonds. Saturation of the double bonds gives the tetrahydromethine, the monomethiodide of which on Hofmann degradation yields trimethylamine and des-*N*(*a*)-emetinetetrahydromethine, $C_{30}H_{43}O_4N$, which is split by oxidation to 6-ethylveratric acid and an acid $C_{19}H_{29}O_4N$. Thus des-*N*(*a*)-emetinetetrahydromethine can be written as (LXXVI), *N*-methylemetinetetrahydromethine as (LXXVII), and emetine as (LXXVIII) (4). The alternative structure (LXXIX) for emetine need not be considered as the alkaloid contains only one C—Me group, which can be otherwise accounted for.

Hydrogenation of the tetrahydromethine (LXXVII) gives the hexa-

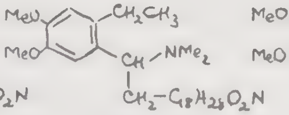




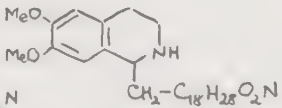
(LXXV)



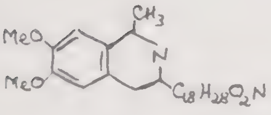
(LXXVI)



(LXXVII)



(LXXVIII)



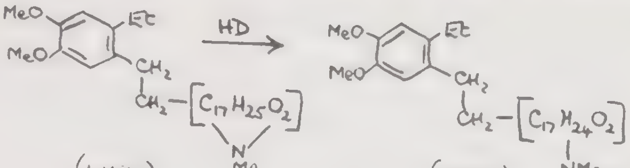
(LXXIX)

hydromethine (LXXX) which on Hofmann degradation yields a base, des-*N*(*a*)-emetinehexahydrobismethine (LXXXI), showing that the tertiary nitrogen of emetine must be common to two rings. Oxidation of the bismethine (LXXXI) affords 6-ethvlveratric acid (LXXV) and an acid $C_{20}H_{33}O_4N$, (LXXXII), so (LXXXI) may be expanded to (LXXXIII) for the bismethine (3).

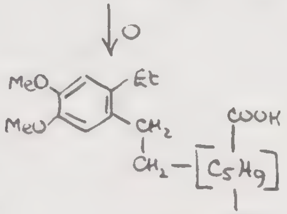
As the double bond and CH_3CH_2— group of (LXXXIII) appear only after Hofmann degradation of emetine (the CH_3CH_2— group first as $CH_2{=}CH$—) the tertiary nitrogen atom of emetine must be linked in the alkaloid to the carbon atoms numbered 1 and 2 in formula (LXXXIII) (the alternative linkage to carbon atoms 3 and 4 need not be considered as emetine contains only one C—Me group which may be otherwise accounted for). Combining the evidence so far obtained, therefore, emetine can be formulated as (LXXXIV).

Reduction of the bismethine (LXXXIII) followed by Hofmann degradation affords a nitrogen-free product that must contain the system $—C{=}CH_2$ as it gives formaldehyde on ozonolysis (25); accordingly the group (C_5H_9)-N in (LXXXIII) and (LXXXIV) can be expanded to (C_4H_7)-CH_2-N.

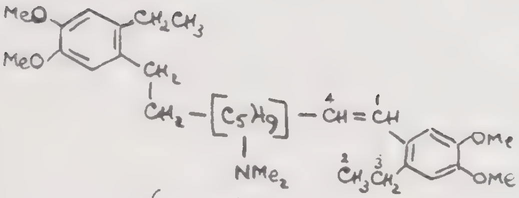
Hofmann degradation of the bismethine (LXXXIII) involves migration of the initially produced double bond into conjugation with the double bond already present, the nitrogen-free product being (LXXXV); this on ozonolysis furnishes an unsaturated aldehyde (LXXXVI) which on hydrogenation gives (LXXXVII), identical with material of this structure prepared by synthesis (28,17). The diene (LXXXV) must thus contain the system (LXXXVIII), which could arise from any of the part-structures (LXXXIX), (XC), and (XCI), the double bond first appearing in the position shown by the dotted line and migrating as shown by the arrow. On this evidence, therefore, three



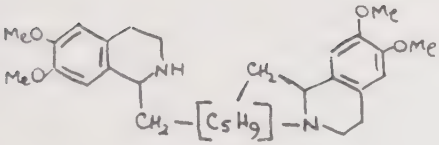
(LXXX) (LXXXI)



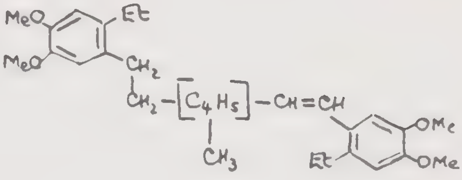
(LXXXII)



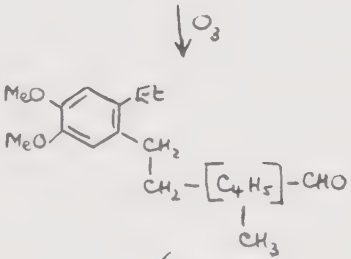
(LXXXIII)



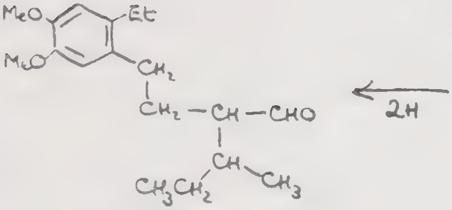
(LXXXIV)



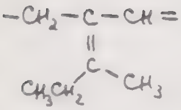
(LXXXV)



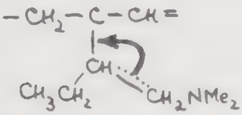
(LXXXVI)



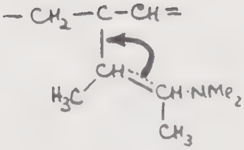
(LXXXVII)



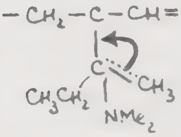
(LXXXVIII)



(LXXXIX)



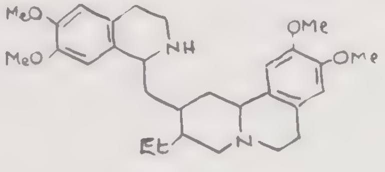
(XC)



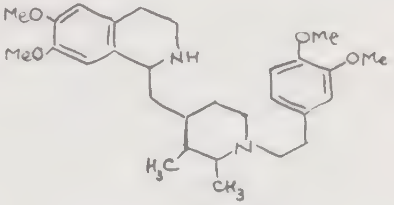
(XCI)

structures, (XCII), (XCIII), and (XCIV), are possible for emetine. Of these (XCIII) and (XCIV) can be ruled out, as emetine contains only one C—Me group, and the structure (XCII) for the alkaloid is further supported by the formation of the pyridine derivative (XCV), which may be oxidized to the acid (XCVI) by the dehydrogenation of the hexahydromethine (LXXX) (3).

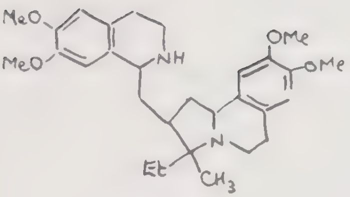
Emetine has been synthesized by the route (XCVII) → (CI) → (XCII).



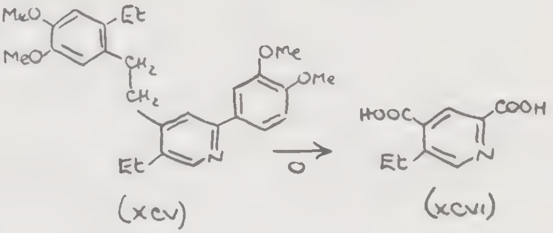
(XCII)

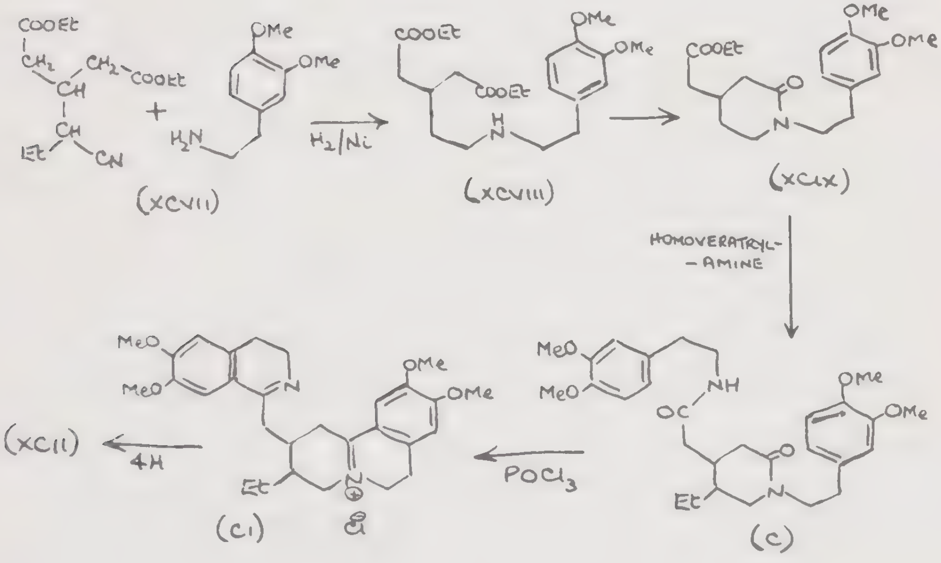


(XCIII)



(XCIV)





B. The Rubremetinium Salts.

Mild oxidation of emetine gives rise to the rubremetinium salts, containing the cation $C_{29}H_{33}O_4N_2^{\oplus}$ which is very highly colored. This cation has the structure (CII) and has a mesomeric system similar to that of a cyanine dye. Reduction of the salts affords two diastereoisomers, the α- and β-dihydrorubremetines (CIII), differing sterically at the asymmetric carbon atom (asterisked in CIII) generated during the reduction.

The oxidation of the bisdihydroisoquinolylpropane (CIV) with mercuric acetate gives a colorless base (CV), the salts of which (CVI) are bright red and have ultraviolet spectra almost identical with the spectrum of rubremetinium bromide (2).

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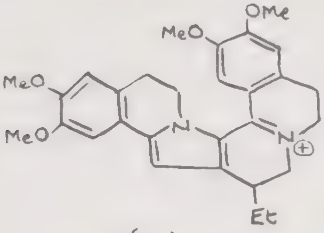
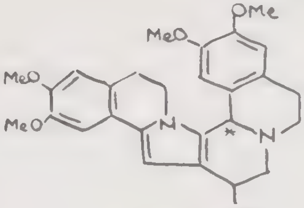
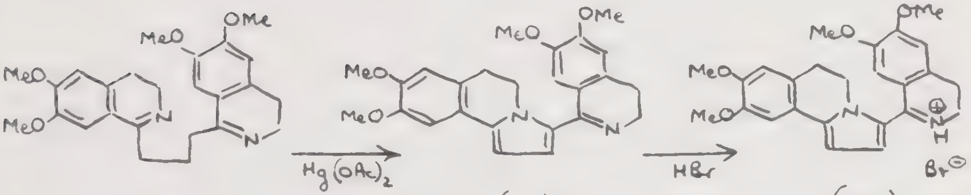


(CII)



(CIII)



(CIV) (CV) (CVI)

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ALKALOIDS OF THE MORPHINE GROUP

The alkaloids of the morphine group have been subjected to more study than those of any other group, partly because of the remarkable analgesic properties of morphine and many of its derivatives, and partly because the alkaloids of this group undergo a wide variety of molecular transformations. The group consists of five closely related bases, morphine, codeine, neopine, thebaine, and oripavine, and two bases of a somewhat different type, sinomenine and hasubanonine.

1. THE CYCLIC ETHER SUBGROUP

Morphine, Codeine, and Thebaine (XXIII).

The compositions $C_{17}H_{19}O_3N$ (59), $C_{18}H_{21}O_3N$ (2), and $C_{19}H_{21}O_3N$ (3), respectively, were established for these bases in 1852. Morphine is a phenol and it may be methylated at the phenolic group to give codeine (36). Both these bases also contain an alcoholic group, the —OH of which may be replaced by halogens (62,80,82). This must be a secondary alcoholic group since codeine can be oxidized to a ketone, codeinone (1,20), which is also obtained by the acid hydrolysis of thebaine (48), showing that the latter alkaloid is the methyl ether of an enolic form of codeinone. The relationship between the three bases is thus clear.

The alkaloids contain a third oxygen atom, which is remarkably inactive under a variety of conditions and was soon recognized as part of a cyclic ether system. Morphine and codeine contain one double bond and thebaine two, but the reduction of thebaine is a

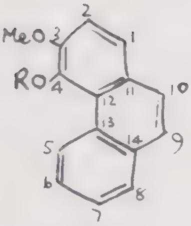
complicated process (4). The mode of linkage of the nitrogen atom is shown by exhaustive methylation; codeine methiodide is degraded by alkali to a base, α-codeimethine (37), showing that the nitrogen is contained in a ring. The further degradation of this base led to the recognition of the basic structure of the alkaloids.

When α-codeimethine is heated with alkalis it suffers a double bond shift giving an isomer, β-codeimethine (58). These bases are degraded by heating with acetic anhydride to acetylmethylmorphol (I, R = Ac) (85). This is a phenanthrene derivative, and can be oxidized to a 9,10-quinone without loss of groups, showing that no substituents are present in the 9 and 10 positions. The structure of acetylmethylmorphol was demonstrated by conversion into 3,4-dimethoxyphenanthrene (I, R = Me) (13), synthesized as shown, (II) ⟶ (IV) ⟶ (I, R = Me) (68). The —OAc group of (I, R = Ac) represents the residue of the codeine cyclic ether system.

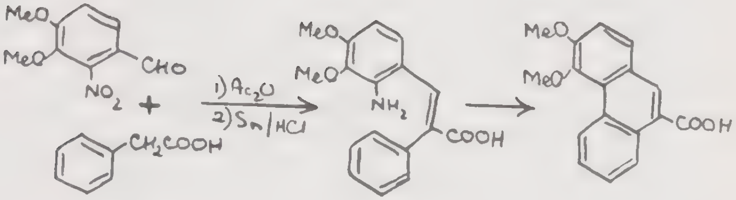
The groups $—C_2H_4—$ and $—NMe_2$ are lost during the acetolysis of α-codeimethine, and the same thing occurs during further Hofmann degradation, the final product being methylmorphenol (V) (55). The location of the 4,5-oxide bridge was shown by alkali fusion of methylmorphenol, when 3,4,5-trihydroxyphenanthrene (VI) was obtained; this was identified by conversion into the trimethoxy compound (84,65).

The position of the alcoholic group was determined by the acetic anhydride degradation of the methiodides of codeinone and thebaine, the products being 3-methoxy-4,6-diacetoxyphenanthrene (VII, R = Ac) and 3,6-dimethoxy-4-acetoxyphenanthrene (VII, R = Me) (47,83), and these were identified by conversion into 3,4,5-trimethoxyphenanthrene, identical with an authentic specimen (70). Codeine may thus be represented by the part-structure (VIII), morphine being the corresponding phenol.

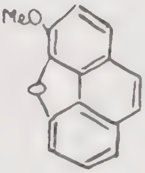
The nitrogen atom was shown to be attached at position 9 or 10 as follows. Oxidation of codeine with chromic acid affords some hydroxycodeine (1), and Hofmann degradation of this gives a ketocodeimethine in which the oxygen appears as a carbonyl group, and when this is heated with acetic anhydride it yields a methoxydiacetoxyphenanthrene that loses an acetoxy group on oxidation to a quinone. The new acetoxy group in the phenanthrene, and hence the



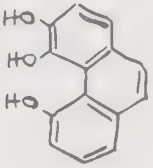
(I)



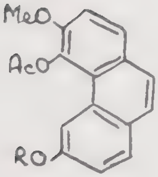
(II) (III) (IV)



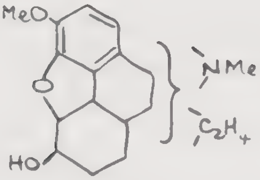
(V)



(VI)



(VII)



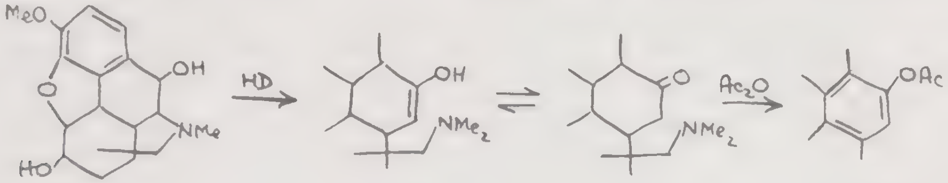
(VIII)

new hydroxyl group in hydroxycodeine, must therefore be at position 9 or 10, and since this group is converted into a carbonyl group during Hofmann degradation, a double bond must be introduced at position 9,10 during scission of the nitrogen ring, and the nitrogen must accordingly be linked to C—9 or C—10, see (IX) ⟶ (XIII). No positive proof of attachment at C—9 rather than C—10 was obtained until the morphine skeleton was synthesized. The point of attachment of the carbon end of the nitrogen-containing side chain remained a problem for many years.

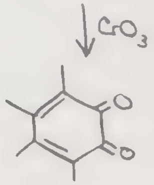
When morphine is heated with concentrated hydrochloric acid apomorphine is formed (see below) and this was soon allotted the structure (XIV) (Chapter 4), and on this basis Pschorr suggested the structure (XV) for morphine (66); this was modified to (XVI) by Knorr to account for the fact that ketocodeimethine is not a naphthol. However, the possibility of the carbon end of the side chain being attached at C—8 is eliminated by a study of the isomeric codeines.

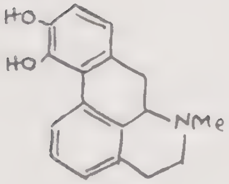
Hydrolysis of the halogenocodides affords three isomers of codeine, isocodeine, ψ-codeine, and allo-ψ-codeine (52,54,60). Codeine and isocodeine differ only in the steric arrangement of the —CH(OH)— group, as they give the same codeinone; ψ-codeine and allo-ψ-codeine also form an epimeric pair giving the same ψ-codeinone on oxidation. When ψ-codeinone is heated with acetic anhydride it is degraded to 3-methoxy-4,8-diacetoxyphenanthrene (VII, R = Ac), identified by conversion into 3,4,8-trimethoxyphenanthrene (49,51). ψ-Codeinone therefore contains a C=O group at C—8 and attachment of the side chain at this point is impossible.

For many years ψ-codeinone was believed to have a $—CH_2—$ group at C—7, leaving only C—5, C—13, and C—14 as possible points of attachment of the side chain. On the grounds that thebenine, a rearrangement product of thebaine, still contains the side chain attached at C—5, Knorr and Hörlein proposed as 9,5-bridged structure (XVIII) for codeine (51). This, however, necessitates the formulation of β-codeimethine as a derivative of naphthalene, which is at variance with the properties of this base; (XVIII) was accordingly modified to (XIX) by Wieland (86).



(IX) (X) (XI) (XII)





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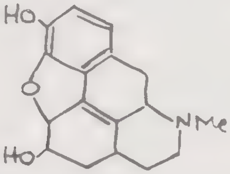

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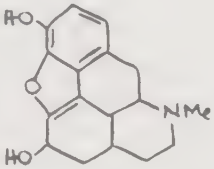
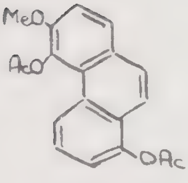
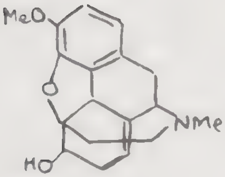


(XVI)

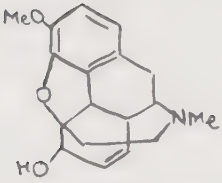
(XIII)



(XVII)



(XVIII)



(XIX)

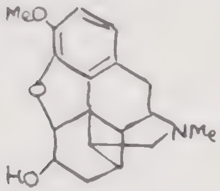
In 1923 Gulland and Robinson in a new survey of the evidence noted that the most striking and unique property of the morphine alkaloids is their tendency to lose the nitrogen-containing side chain during degradation giving phenanthrene derivatives, and they realized that this property is due to some peculiarity of the molecule which any adequate formula must explain. They stated:

"The driving force behind the change is doubtless the tendency to produce an aromatic nucleus, for extrusion of the side chain is never observed independently of the formation of an aromatic system. *The formation of the phenanthrene derivative cannot take place for structural reasons unless the ethanamine chain is displaced.*"

On these grounds they proposed attachment of the side chain at an angular position so that its extrusion is a necessary part of aromatization, and of the two possible positions C—13 was selected. These suggestions were embodied in the camphane formulas (XX) and (XXI) for codeine and thebaine (38). These structures were subsequently modified by the same authors (39) following a study of 14-hydroxycodeinone, which was found to contain the system O═C—CH═CH—C—OH, and on the basis of the proposed mechanism of the production of this base by the action of hydrogen peroxide on thebaine, (XXIV) ⟶ (XXVI), thebaine was allotted the structure (XXIII) and codeine (XXII).

The arrangement (XXIV) of the conjugated double bonds in thebaine is supported by the fact that the base condenses with maleic anhydride (Diels-Alder reaction) giving an adduct (XXVII) that cannot be hydrolyzed to a ketone (76). The alternative arrangement (XXVIII) would give the enol ether (XXIX) which would yield a ketone on hydrolysis.

Direct evidence was sought by Schöpf (73) for the attachment of the side chain at C—13 by the Beckmann transformation of dihydrocodeinone oxime. This would give an aldehyde on the basis of a C—13 attachment of the side chain, (XXX) ⟶ (XXXI), whereas a ketone would result from a C—5 attachment, (XXXII) ⟶ (XXXIII). Unfortunately the hoped for proof was not directly obtained and the transformation product was only identified as (XXXI) after a series of further degradations (73) (see ref. 4, p. 175).



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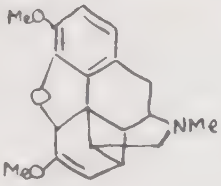

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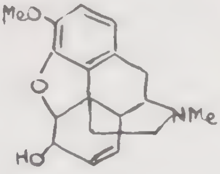

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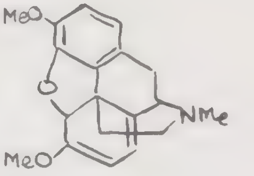

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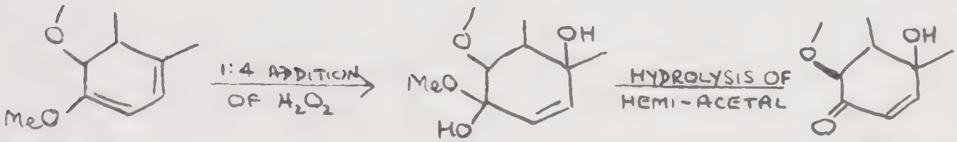
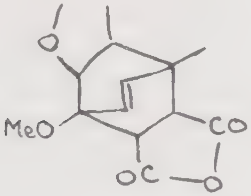
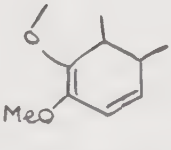


(XXIV) (XXV) (XXVI)



(XXVII)



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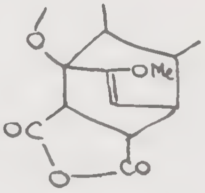

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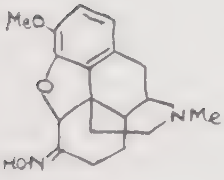
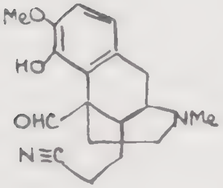
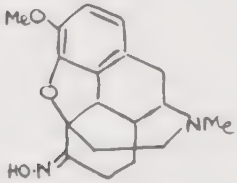


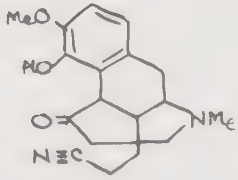
(XXX)



(XXXI)



(XXXII)



(XXXIII)

The Gulland-Robinson formulas give satisfactory explanations of all the properties of the morphine alkaloids. The $\alpha \longrightarrow \beta$-codeimethine change is formulated as (XXXIV) → (XXXV). ϵ-Codeimethine (XXXVII), derived from ψ-codeine (XXXVI), cannot achieve a similar increase in conjugation and no isomerization occurs. The transformation of codeine through the halogenocodides to iso, ψ-, and allo-ψ-codeine is analogous to the conversion of geraniol (XXXVIII) to linaloöl (XXXIX).

B. Neopine (XL).

This base, isolated from the final mother liquors of the extraction of morphine from opium, is an isomer of codeine differing from that base only in the position of the double bond, as is shown by its conversion into dihydrocodeine on catalytic reduction. The position of the double bond is clearly shown by the production of β-codeimethine (XXXV) on degradation of neopine methiodide; neopine is therefore (XL) (81).

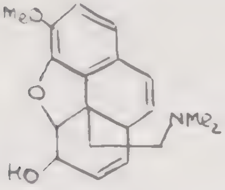
C. Oripavine.

This alkaloid, which is found in the oriental poppy, is the phenolic analog of thebaine, which it gives on methylation (46).

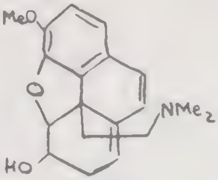
2. THE TOTAL SYNTHESIS OF MORPHINE

The first synthesis of the carbon-nitrogen skeleton present in morphine was achieved by Grewe using a reaction analogous to the final step in the Bogert-Cook synthesis of phenanthrene derivatives. The base (XLVIII), prepared as shown in (XLI) → (XLVIII), was heated with phosphoric acid, the product being *N*-methylmorphinan (XLIX), having the same configuration at the three asymmetric carbon atoms as morphine (33,34). Similarly, (L) was cyclized by heating with hydrochloric acid, demethylation occurring at the same time, the product being (±)-tetrahydrodesoxycodeine (LI), identical with the racemate obtained by mixing (+) and (−)-tetrahydrodesoxycodeine obtained from the sinomenine and thebaine series, respectively (35). Morphine has not been synthesized in this way.

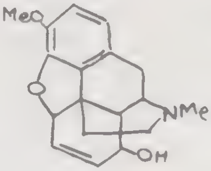
The total synthesis of morphine was first achieved by Gates, after preliminary work on unsubstituted compounds, as shown in the



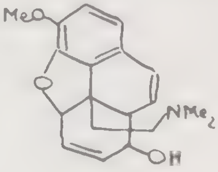
(XXXIV)



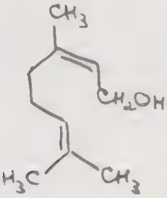
(XXXV)



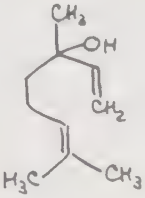
(XXXVI)



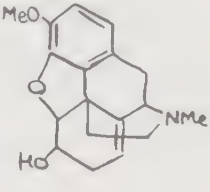
(XXXVII)



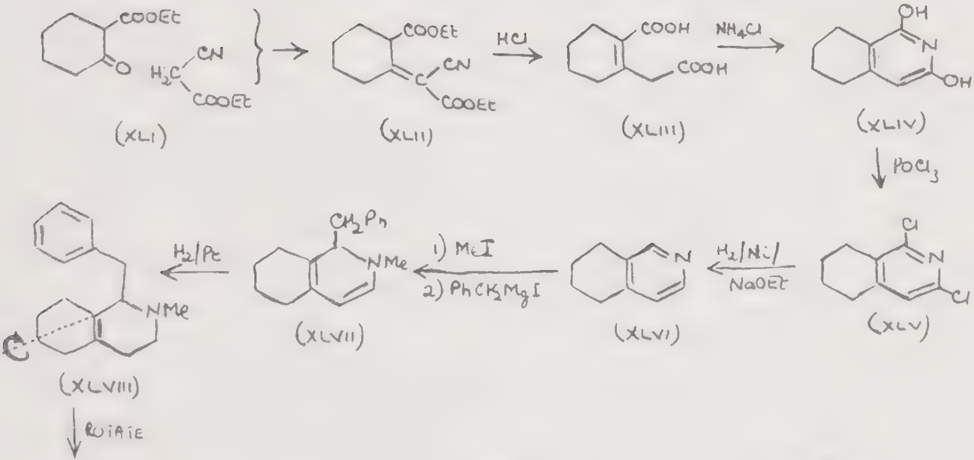
(XXXVIII)



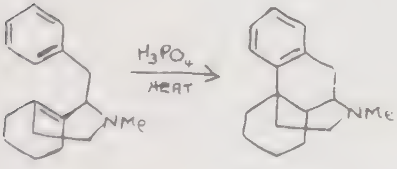
(XXXIX)



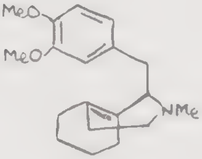
(XL)



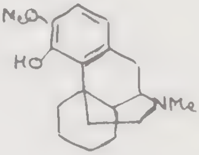
(XLI) (XLII) (XLIII) (XLIV) (XLV) (XLVI) (XLVII) (XLVIII)



(XLVIII a) (XLIX)

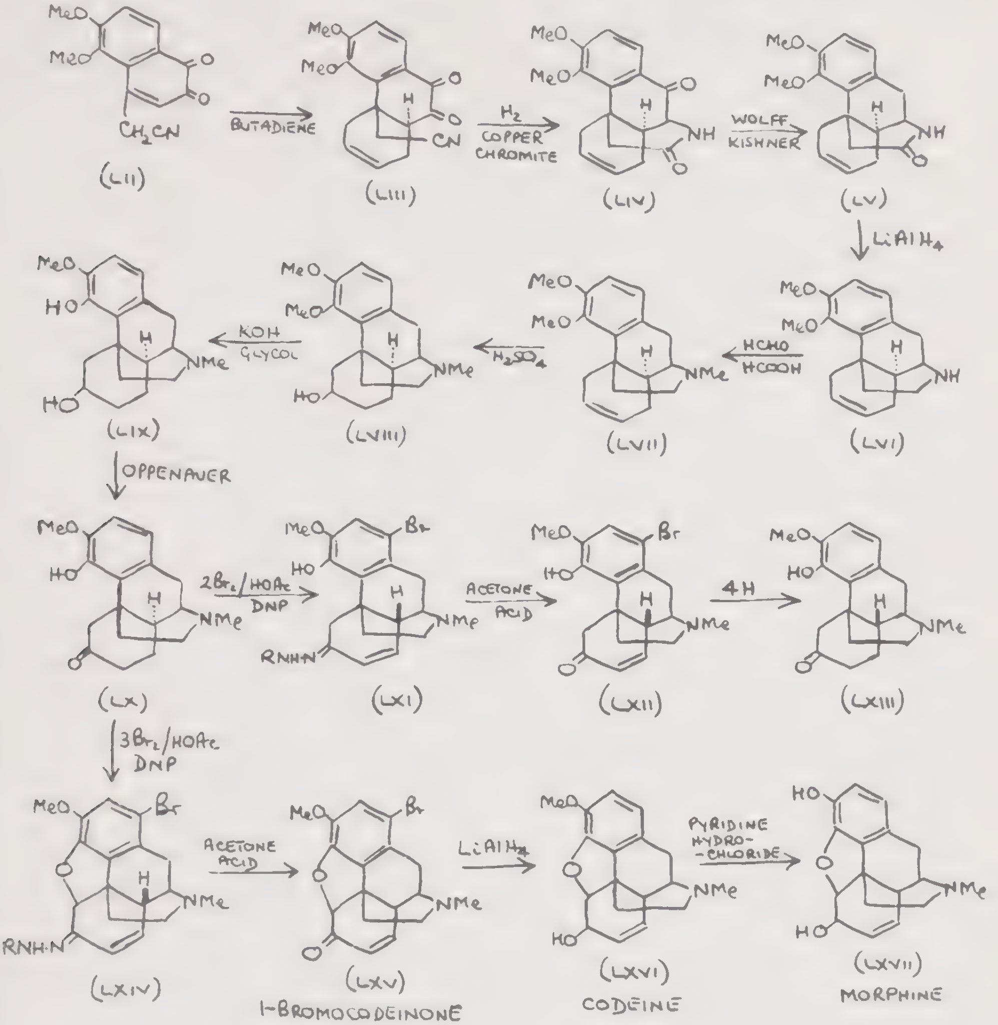


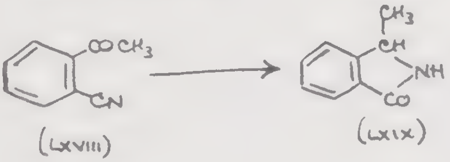
(L)



(LI)

formulas (LII) → (LXVII) (18,21). The reductive cyclization (LIII) → (LIV) is analogous to the reductive cyclization of *o*-cyanoacetophenone (LXVIII) to (LXIX) (21). The sequence of processes up to (LVII) afforded a base having the opposite configuration at C—14 to that found in morphine, and (LVII) was found to be identical with β-Δ^6-dihydrodesoxycodeine methyl ether (19). The conversion of this into morphine involved an inversion at C—14 at one stage, and this was accomplished as shown in (LX) → (LXIV) and (LX) → (LXI), the inversion occurring with remarkable ease in the 2,4-dinitrophenylhydrazones (20).


(LII)
BUTADIENE
(LIII)
H2
COPPER CHROMITE
(LIV)
WOLFF KISHNER
(LV)
LiAlH4
(LVI)
HCHO HCOOH
(LVII)
H2SO4
(LVIII)
KOH GLYCOL
(LIX)
OPPENAUER
(LX)
2Br2/HOAc DNP
(LXI)
ACETONE ACID
(LXII)
4H
(LXIII)
3Br2/HOAc DNP
(LXIV)
ACETONE ACID
(LXV)
1-BROMOCODEINONE
LiAlH4
(LXVI)
CODEINE
PYRIDINE HYDRO-CHLORIDE
(LXVII)
MORPHINE


COCH3
CN
(LXVIII)
CH3
CH
NH
CO
(LXIX)

A second synthesis, involving no epimerization at any stage has been developed by Ginsburg (11,12,22,23). This synthesis, (LXX) → (LXXXV), involves frequent inactivation of one of two carbonyl groups by conversion into the cyclic acetal with ethylene glycol, thus enabling modifications to be made at the other center of reactivity. The end-product of the synthesis is dihydrothebainone (LXXXV), and as this has been converted into morphine (20) the sequence can be regarded as a total synthesis of the alkaloid.

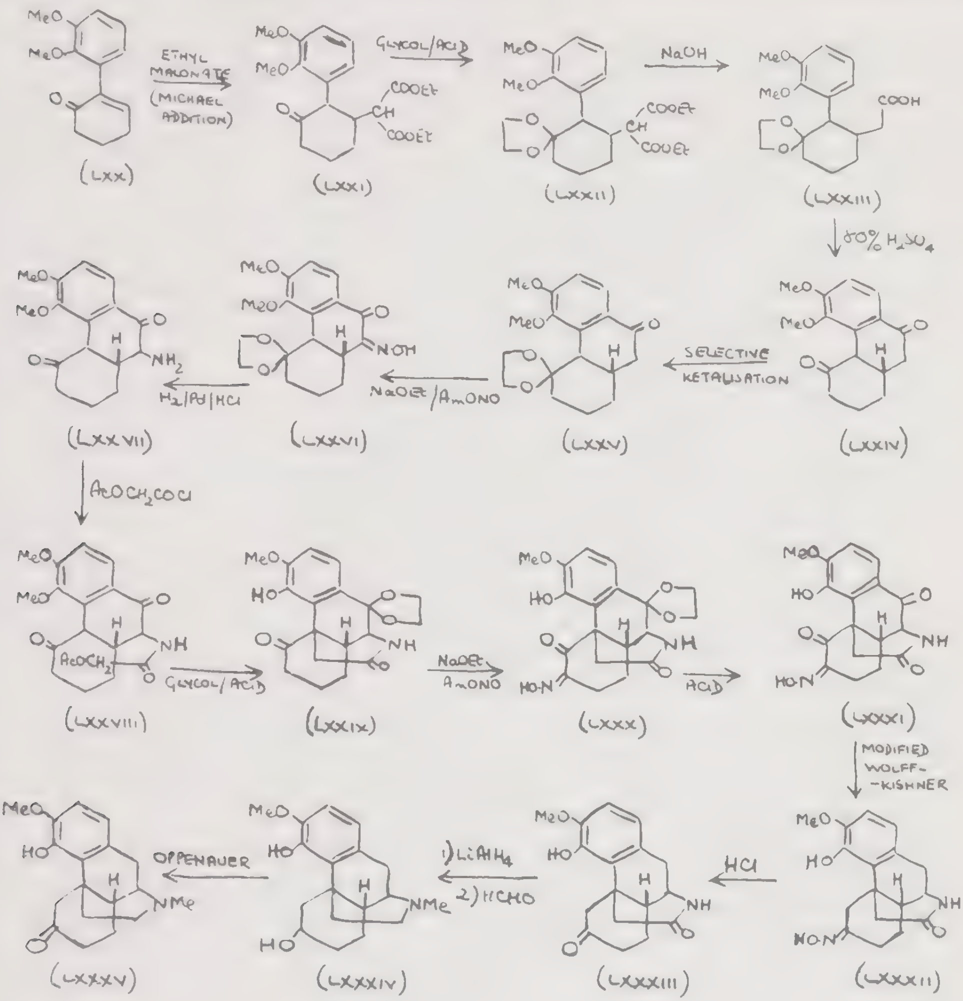
3. MOLECULAR REARRANGEMENTS OF THE ALKALOIDS

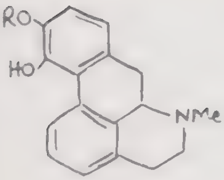
A. When morphine is heated with concentrated hydrochloric acid at 140° dehydration and rearrangement occurs, the product being apomorphine (LXXXVI, R = H) (61); codeine may be similarly converted into apocodeine (LXXXVI, R = Me) (78). The degradation and synthesis of apomorphine dimethyl ether are discussed in Chapter 4.

B. A similar rearrangement takes place when thebaine is heated with concentrated hydrochloric acid at 100°; in this case thebaine can achieve the aporphine structure without the loss of the oxygen function at C—6 and the product of the rearrangement is morphothebaine (LXXXVII) (42). The degradation and synthesis of morphothebaine dimethyl ether are discussed in Chapter (4).

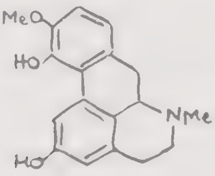
C. A different sort of rearrangement occurs when thebaine is heated for a short time with dilute hydrochloric acid; the product is a phenanthrene derivative, thebenine (LXXXVIII) (41). The positions of the oxygen substituents were demonstrated by exhaustive methylation to 3,4,8-trimethoxy-5-vinylphenanthrene (LXXXIX, R = $CH{=}CH_2$), which was oxidized to the acid (LXXXIX, R = COOH) and subsequently decarboxylated to 3,4,8-trimethoxyphenanthrene (67). The position of the side chain was clearly shown by the reduction of the vinyl compound (LXXXIX, R = $CH{=}CH_2$) to 3,4,8-trimethoxy-5-ethylphenanthrene (LXXXIX, R = Et), identical with an authentic specimen (40).

D. When thebaine is dissolved in concentrated hydrochloric acid an orange-red solution, from which no thebaine can be recovered, is obtained. Reduction of this solution catalytically (10) or with

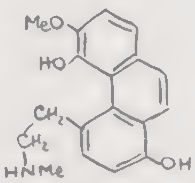




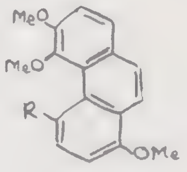
(LXXXVI)



(LXXXVII)



(LXXXVIII)



(LXXXIX)

stannous chloride (69) affords metathebainone (XC) (74). This base gives an orange solution in acids and a deep yellow solution in alkalis, and in these respects resembles *o*-hydroxybenzylidene acetone (XCI). In addition it behaves as an α,β-unsaturated ketone, and must therefore contain the system —C═C—C═O linked to the guaiacol nucleus; to accommodate this the side chain must have migrated, and it is placed at the angular position C—14 on the basis of the degradation of metathebainone methyl ether methine (XCII) to 3,4-dimethoxyphenanthrene with extrusion of the side chain on heating with acetic anhydride (56). The true thebainone (XCIII), in which the side chain retains its original position, may be isolated from the products of the stannous chloride reduction of thebaine (75); it is also accessible in other ways (17).

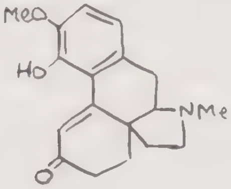
E. Treatment of thebaine with phenylmagnesium bromide affords a phenolic base, phenyldihydrothebaine (64), a compound of considerable theoretical interest. Largely as a result of the work of Small and his co-workers (77,79) it is known that this base exists in four optically active forms: (+)-α, (–)-α, (+)-δ, and (–)-δ; of these (+)-α and (+)-δ appear in the initial Grignard reaction and they are partly isomerized by heat to (–)-α and (–)-δ. It is clear that the original base contains two, and only two, centers of dissymmetry; one of these, responsible for the $\alpha:\delta$ isomerism, is eliminated when the nitrogen ring is opened between the nitrogen and the original C—9 of thebaine, but the other center persists through exhaustive methylation to nitrogen-free products, and this is the center about which racemization can be effected by heat.

Phenyldihydrothebaine, which has the composition $C_{25}H_{27}O_3N$, has a number of remarkable properties as follows.

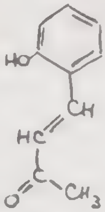
(*a*) It is remarkably resistant to hydrogenation; if the reaction is forced it results in reductive scission of the nitrogen-containing ring giving a secondary amine, phenyltetrahydrothebaimine.

(*b*) It is very stable to hydrolysis and may be demethylated by hydrobromic acid to a trihydric phenol, which gives phenyldihydrothebaine methyl ether on remethylation.

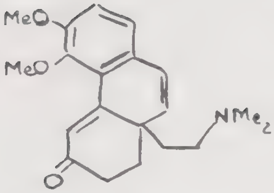
(*c*) The side chain is retained as a vinyl group during exhaustive methylation; this is not encountered with other morphine alkaloids in a comparable state of oxidation.



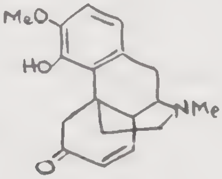
(xc)



(xci)



(xcii)



(xciii)

(*d*) There is partial racemization at C—9 during entry of the phenyl group, and racemization may be effected by heat at the only other center of dissymmetry.

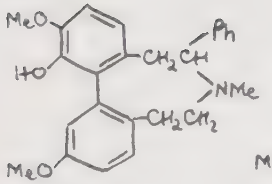
The obvious explanation of points (*a*)-(*c*) is that the near-aromatic ring of thebaine, which bears the hydrolyzable methoxyl group, has become fully aromatic in phenyldihydrothebaine. Small, however, rejected this view on the grounds it would render an explanation of the optical activity of phenyltetrahydrothebaimine impossible, and that the ultraviolet spectra of phenyldihydrothebaine and numerous other morphine derivatives gives no indication of the appearance in the new base of a second aromatic nucleus in conjugation with that already present in thebaine. He was unable to offer a satisfactory solution to the problem and therefore questioned the validity of the Gulland-Robinson formulas for morphine and thebaine.

The puzzle was satisfactorily solved by Robinson, and the author was associated with him in the final proof (71,72,9). The solution was based on the hypothetical aromatization of ring—C of thebaine and the other conclusions followed logically from this. The processes leading to the nitrogen-free product $C_{24}H_{22}O_2$ may be represented in the form

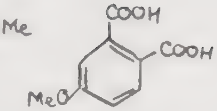
$$—C—C—NMe—C—C— \rightarrow —C{=}C + NMe_3 + C{=}C—$$

and the presence of the two double bonds in the end-product is easily demonstrated. Of the twenty carbon atoms of phenyldihydrothebaine one is present in an —NMe— group, now lost, two in —OMe groups, and, by hypothesis, eighteen are present in three benzene rings. Hence the nitrogen-free product cannot contain an asymmetric carbon atom and must owe its optical activity to dissymmetry due to restricted rotation in a diphenyl system.

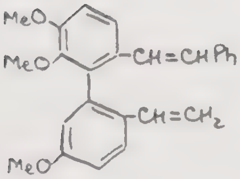
On these grounds, and on the basis of a reasonable mechanism for the Grignard reaction, the structure (XCIV) was suggested for phenyldihydrothebaine, and proved by oxidation of the base to 4-methoxyphthalic acid (XCV) and by oxidation of the nitrogen-free product (XCVI) to trimethoxydiphenic acid (XCVII), identical with an authentic specimen (9). Small's objection based on ultraviolet spectra is disposed of by the fact that noncoplanar diphenyls do *not* exhibit typical diphenyl absorption (63,64). The structure (XCI) is



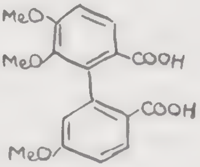
(XCIV)



(XCV)



(XCVI)



(XCVII)

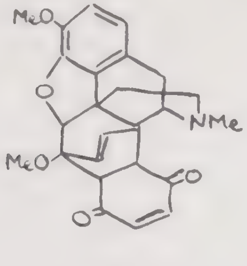
perfectly satisfactory; examination of models shows that the nine-membered ring allows the aromatic nuclei to be disposed at right angles or at any other angle without strain, ready interconversion of the two extremes being hindered by the hydrogen atoms and the phenyl group.

F. When thebaine is treated with benzoquinone Diels-Alder reaction occurs giving (XCVIII), which readily enolizes to the hydroquinone (XCIX). The hydroquinone, on heating with concentrated hydrochloric acid is rearranged to flavothebaone (76), which has been the subject of a detailed investigation by the author and his co-workers. Flavothebaone is now believed to have the structure (C) (5,8); on degradation it undergoes a series of further molecular rearrangements (5,8). Benzflavothebaone, derived from 1,4-naphthoquinone, has also been prepared (6).

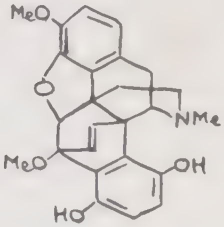
4. THE REARRANGEMENT MECHANISMS

A. Morphine → Apomorphine.

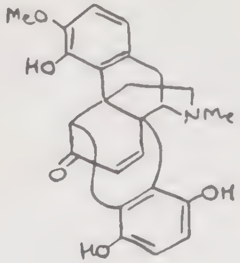
This process, in common with all those outlined above, may be regarded as being initiated by attack by a positive ion at the cyclic ether oxygen atom. Attack of morphine by a proton gives the carbonium ion (CII), which is transformed into (CIII) and dehydration then gives (CIV); the positive end of the side chain then migrates over the π-orbitals to C—8 and a proton is expelled to give apomorphine (CV). Dehydration could of course occur earlier, e.g., (CI), (CII), (CVI) → (CV).



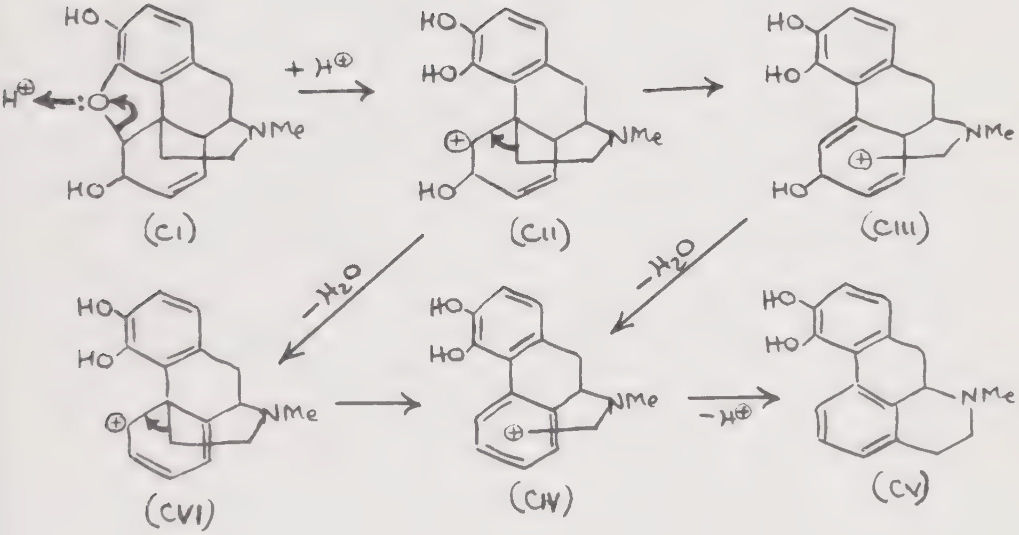
(XCVIII)



(XCIX)



(C)



B. Thebaine → Morphothebaine.

This rearrangement could proceed in a similar way. Thebaine could be hydrolyzed to codeinone, the enol form of which could then suffer the sequence of reactions (CVII) → (CX). Alternatively the sequence could be (CXI) → (CXIV), in which (CXIII) could be the intermediate responsible for the orange color of thebaine in concentrated hydrochloric acid. Conversion of (CXIII) into morphothebaine (CXIV) is then analogous to the conversion of santonin (CXV) into desmotroposantonin (CXVI), which also occurs under acid conditions. Reduction of the isolated double bond of (CXIII) would give metathebainone (CXVII), which is formed by the reduction of thebaine in concentrated acid solution.

C. Thebaine → Thebenine.

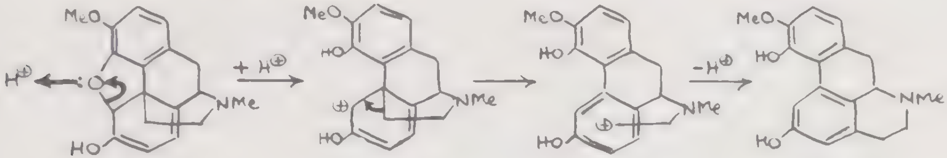
The intermediate (CXIII) is again postulated in this rearrangement. It could add a proton (CXVIII) giving the Schiff's base quaternary salt (CXIX), which would be immediately hydrolyzed to the aldehyde (CXX). Rotation of one of the aromatic nuclei, followed by cyclodehydration would then give thebenine. Robinson has always attached considerable importance to this theory, for the processes will not work plausibly if the nitrogen atom is attached at C—10 in thebaine, or if the side chain is attached at C—5.

D. Thebaine → Metathebainone.

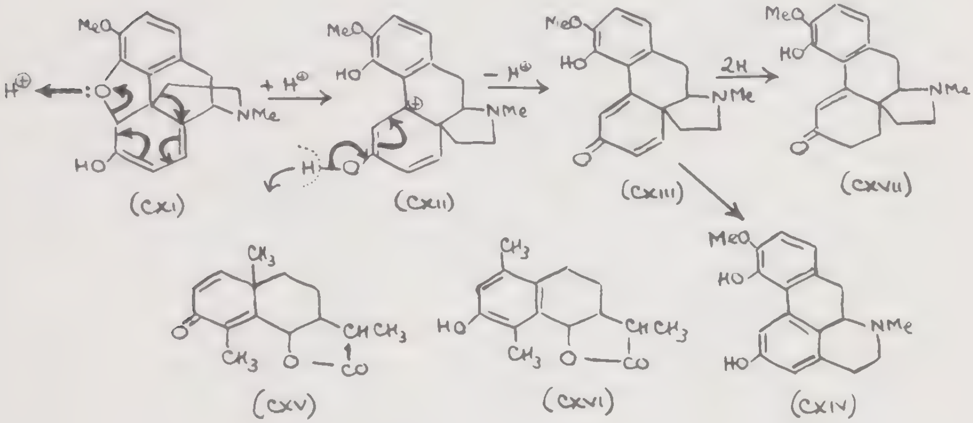
The intermediate (CXIII) postulated above could easily suffer reduction at the exposed double bond giving metathebainone (CXVII).

E. Thebaine → Phenyldihydrothebaine.

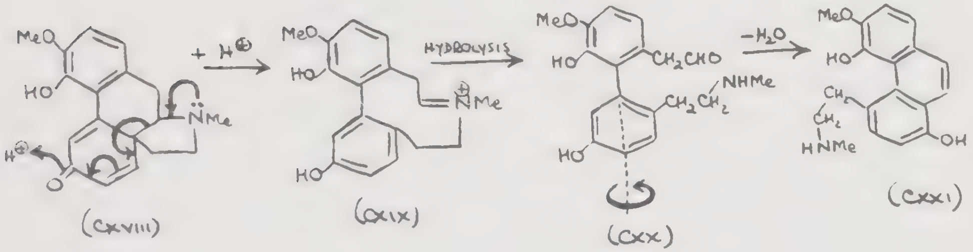
This change is initiated by attack by $MgBr^+$ at the cyclic ether oxygen atom, followed by the electronic shifts shown in (CXXII) giving the Schiff's base quaternary salt (CXXIII), which is converted into phenyldihydrothebaine (CXXIV) by the attack of a phenyl anion. The iodide of (CXXIII) is obtained by treating thebaine with anhydrous magnesium iodide; it gives phenyldihydrothebaine on treatment with phenylmagnesium bromide (9). In this way the asym-



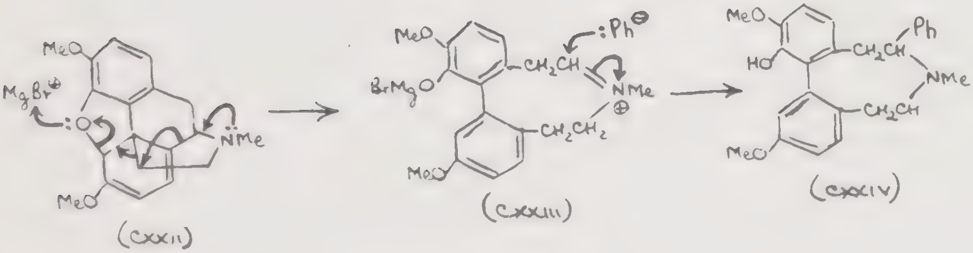
(CVII) (CVIII) (CIX) (CX)



(CXI) (CXII) (CXIII) (CXVII) (CXV) (CXVI) (CXIV)



(CXVIII) (CXIX) (CXX) (CXXI)



(CXXII) (CXXIII) (CXXIV)

metric carbon atom appears in both configurations (α and δ isomerism); the diphenyl system is configured in one sense only.

F. Thebainehydroquinone → Flavothebaone.

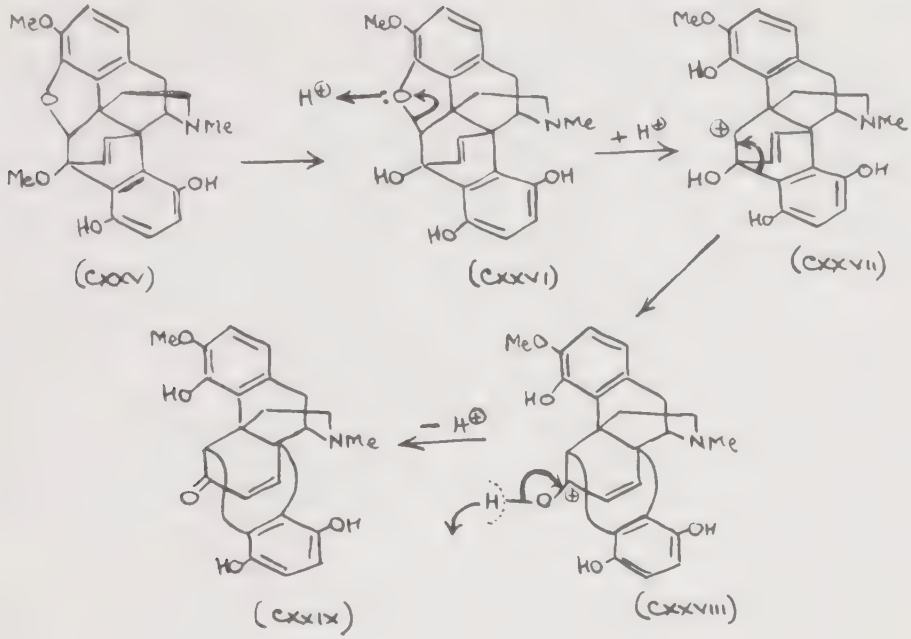
The first stage of this rearrangement is presumably the hydrolysis of the C—6 methoxyl group of (CXXV); this is the methyl ether of a tertiary, allylic, benzylic alcohol, so demethylation should occur with ease. The product (CXXVI) is then attacked by a proton giving (CXXVII), which is the same sort of ion as occurs as an intermediate in the pinacol-pinacolone transformation, in which aromatic groups migrate preferentially. Accordingly the hydroquinone nucleus migrates from C—6 to C—5, giving (CXXVIII), loss of a proton from which affords flavothebaone (CXXXIX). In this case there is no call upon the side chain to migrate (4,8).

G. α-Codeimethine → Acetylmethylmorphol.

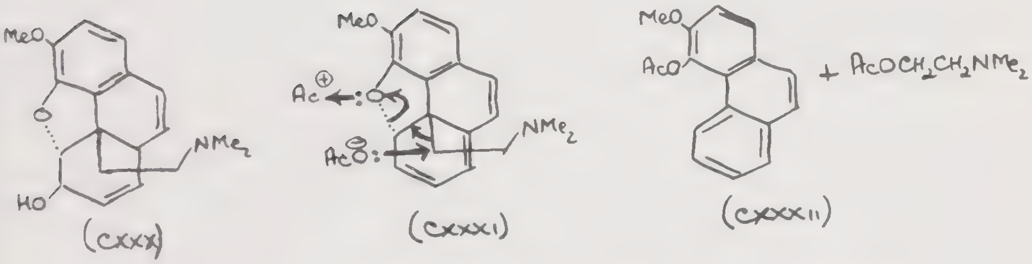
This degradation presumably proceeds by the concerted mechanism (CXXX) → (CXXXII), involving a *trans* elimination of the side chain and opening of the oxide ring.

H. α-Codeimethine → Methylmorphenol.

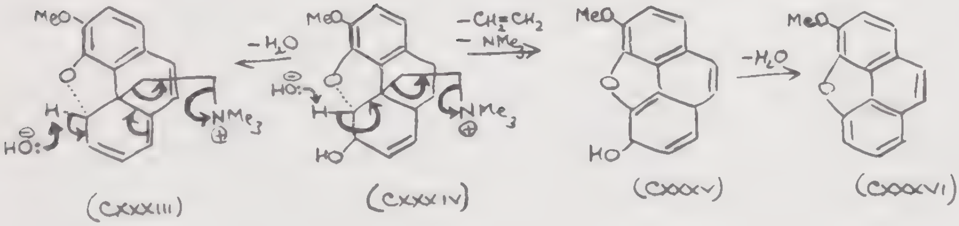
This may involve a difficult *cis* elimination of the side chain and the C—5 hydrogen atom (CXXXIV) → (CXXXV), but this could be avoided if dehydration took place as the first step, for then the electronic shifts could go all the way round the ring as in (CXXXIII) and the stereochemical limitations of simple elimination reactions would not apply.



(CXXV) (CXXVI) (CXXVII) (CXXIX) (CXXVIII)



(CXXX) (CXXXI) (CXXXII)



(CXXXIII) (CXXXIV) (CXXXV) (CXXXVI)

It is interesting to note that although the simple 13-vinyl compounds (CXXXVII) and (CXXXVIII) cannot be obtained from α- and β-codeimethine by Hofmann degradation, they are obtainable by the degradation of the nitrogen oxides. The second product of this reaction, which has been shown to be a general method of systematic degradation, is dimethylhydroxylamine; the process is doubtless one of simple internal cyclic elimination as shown in (CXLI) (7). When a free hydroxyl group is present at position 4 Hofmann degradation occurs with ease, the side chain being retained, even in highly unsaturated compounds, a cyclic ether system being formed. The process is doubtless as outlined (CXXXIX) ⟶ (CL). These ethers are spoken of as being of the thebenone type; thebenone is the ketone (CXLIII) (87). The same type of cyclic ether results from the degradation of the 4-hydroxy-nitrogen oxides, the process doubtless being as shown in (CXLII) (7).

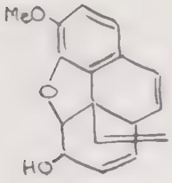
I. Thebaine ⟶ 14-Hydroxycodeinone.

This change doubtless results from the addition of hydrogen peroxide to the conjugated diene system of thebaine, followed by hydrolysis of the resulting hemi-acetal (XXIV), (XXV) ⟶ (XXVI). Thebaine reacts with bromine in a similar way, giving 14-bromcodeinone, which affords 14-hydroxycodeinone on treatment with hydroxylamine (15).

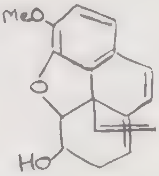
5. BASES NOT CONTAINING THE CYCLIC ETHER SYSTEM

A. Sinomenine (CXLVII).

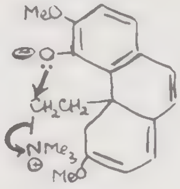
This alkaloid occurs in the Japanese plant *Sinomenium acutum*; it has the composition $C_{19}H_{23}O_4N$, is phenolic, and contains one —NMe— group, two methoxyl groups, and one α,β-unsaturated carbonyl group. Like thebaine, it is very easily converted into phenanthrene derivatives. When the methiodide is heated with benzoic anhydride it is degraded to dibenzoylsinomenol (CXLIV, R = PhCO) (24), identified by conversion into 3,4 : 6,7-tetramethoxyphenanthrene (CXLIV, R = Me), identical with an authentic specimen (28,45). Hydrolysis and ethylation of dibenzoylsinomenol affords 3,7-dimethoxy-4,6-diethoxyphenanthrene (CXLIV, R = Et),



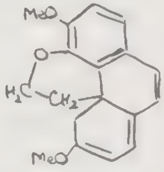
(CXXXVII)



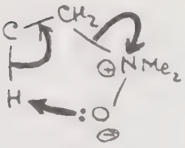
(CXXXVIII)



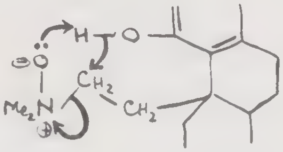
(CXXXIX)



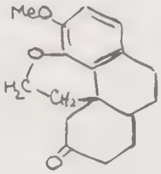
(CXL)



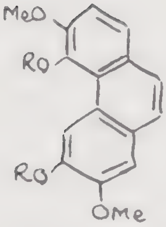
(CXLI)



(CXLII)



(CXLIII)

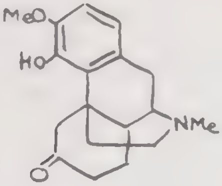


(CXLIV)

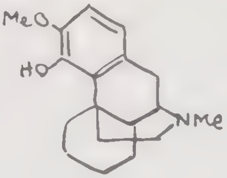
showing that the methoxyl groups in sinomenine are at positions 3 and 7. The loss of the nitrogen-containing side chain during this degradation shows that sinomenine belongs to the morphine group.

When dihydrosinomenine is reduced with sodium amalgam desmethoxydihydrosinomenine (CXLV), the optical antipode of dihydrothebainone obtained from the thebaine series is produced (29). Reduction by Clemmensen's method affords desmethoxydesoxydihydrosinomenine (CXLVI), the optical antipode of tetrahydrodesoxycodeine (25,45). Sinomenine may therefore be allotted the structure (CXLVII) (28), which accounts for all the reactions of the alkaloid.

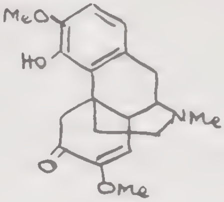
On bromination with two equivalents of bromine sinomenine suffers ring closure of the 4,5-oxide bridge, giving 1-bromosinomeneine (CXLVIII) (26). Sinomenine may be hydrolyzed to sinomeninone (CXLIX), which is an α-diketone (30) and can be oxidized with hydrogen peroxide to sinomeninic acid (CL) (32). 1-Bromosinomeneine may also be hydrolyzed to an α-diketone, 1-bromosinomeneine ketone (CLI) (26), which can be made to undergo benzilic acid rearrangement to 1-bromosinomenilic acid (CLII) (31): oxidation of the last of these yields 1-bromosinomenilone (CLIII) (31), convertible by stages into dihydrosinomenilan (CLIV) and dihydrosinomelan (CLV) (27).



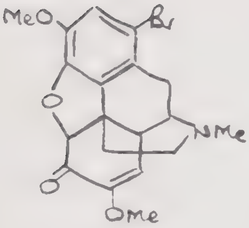
(CXLV)



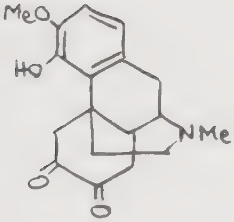
(CXLVI)



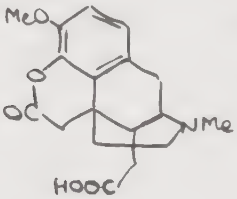
(CXLVII)



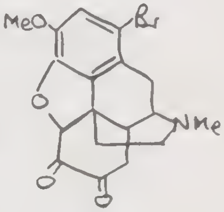
(CXLVIII)



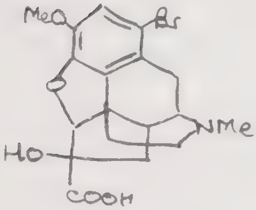
(CXLIX)



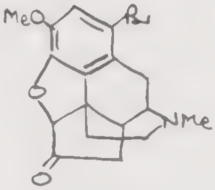
(CL)



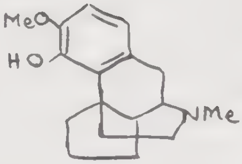
(CLI)



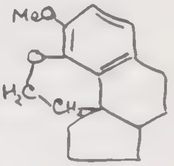
(CLII)



(CLIII)



(CLIV)



(CLV)

B. Hasubanonine (CLVIII).

This alkaloid, $C_{21}H_{27}O_5N$, isolated from *Stephania japonica* Miers, is nonphenolic and contains four —OMe groups, one —NMe— group, and an α,β-unsaturated ketone system. Hofmann degradation is accompanied by demethylation and affords an alkali-soluble methine base $C_{21}H_{27}O_5N$, containing four —OMe groups. This on heating with acetic anhydride loses the nitrogen-containing side chain and water giving acetylhasubanol, which may be hydrolyzed and methylated to 3,4,6,8-tetramethoxyphenanthrene. Color reactions indicate a free *para* position with respect to the phenolic hydroxy group of hasubanol, and this group is accordingly placed at position 8; the alternative position 4 being eliminated by the oxidation of hasubanonine to hemipinic acid. In the belief that the hydroxyl group of hasubanol is derived from the carbonyl group of hasubanonine the alkaloid has been allotted the structure (CLVI), the methine base being (CLVII) and hasubanol (CLVIII) (43,44). The double bond of hasubanonine is resistant to reduction and is therefore presumably fully substituted, thus ruling out a 3,4,5,6,8-substituted formula, but it seems to the author that the published evidence does not exclude the structure (CLVIa) for the alkaloid: this, like (CLVI), would give the methine (CLVII) on Hofmann degradation and demethylation.

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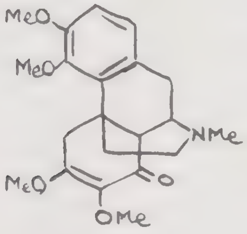
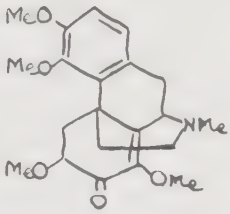
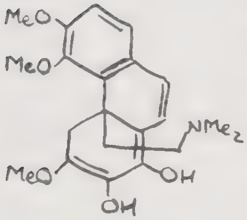


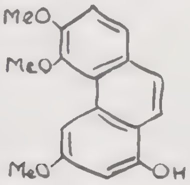
(CLVI)



(CLVIa)



(CLVII)



(CLVIII)

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CHAPTER 6

ALKALOIDS OF THE QUINOLINE GROUP

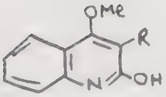
1. FUROQUINOLINE ALKALOIDS

This group consists of alkaloids containing a furane ring and also of alkaloids containing in addition a pyrane ring.

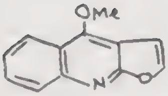
A. Dictamnine (II).

This is the simplest alkaloid of the group; it is found in white dittany root (*Dictamnus albus* L.) and in *Skimmia repens* Nakai. It has the composition $C_{12}H_9O_2N$ (2) and contains one —OMe group. Though unaffected by boiling methyl iodide it reacts with this reagent at 80° giving isodictamnine, which contains —NMe— but no —OMe. With ethyl iodide homoisodictamnine, which contains —NEt—, is obtained. In this respect the alkaloid resembles the 2- and 4-alkylquinolines.

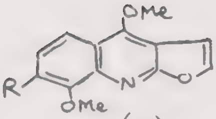
Dictamnine on oxidation gives an aldehyde, dictamnal, $C_{11}H_9O_3N$, and the related acid dictamnic acid. The acid may be demethylated and decarboxylated to 2,4-dihydroxyquinoline, and as it is not identical with 2-methoxy-4-hydroxyquinoline-3-carboxylic acid it must be the 4-methoxy-2-hydroxy compound (I, R = COOH) and dictamnal must be (I, R = CHO). Since the alkaloid contains no hydroxyl or carbonyl group the unidentified oxygen atom must be part of an ether system attached at position 2 of the quinoline system. The aldehyde group of dictamnal is presumably the residue of a $—C{=}C—$ group and the structure (II) may accordingly be assigned to dictamnine (2). Other alkaloids of this group are skimmianine, which can be degraded to 7,8-dimethoxy-2,4-dihydroxyquinoline and may be represented by (III, R = OMe) and γ-fagarine (III, R = H).



(i)



(ii)



(iii)

None of the alkaloids of this group has been synthesized. An attempt to synthesize dictamnine was made as shown in formulas (IV) ⟶ (XI), but cyclization of the oxygen ring apparently proceeded with the 4-hydroxyl group of (VI) giving ψ-dictamnine (XI) as final product (1).*

Alkaloids containing an additional heterocyclic ring are acronidine (XII), or (XIII, R = OMe) and medicosmine (XIII, R = H), or an isomer (11,13).

2. ANGOSTURA ALKALOIDS

A. Cusparine (XV) and Galipine (XIV).

These are two alkaloids of *Galipea officinalis*; they have the compositions $C_{19}H_{17}O_3N$ and $C_{20}H_{21}O_3N$, respectively. Cusparine contains one and galipine three —OMe groups. Both are tertiary bases and give methiodides that on treatment with alkali yield isocusparine and isogalipine, respectively; these bases contain an —NMe— group and one less —OMe group than the parent alkaloids (28,30). Both bases give protocatechuic acid on fusion with potassium hydroxide. Distillation of galipine with zinc dust affords quinoline.

Oxidation of galipine with permanganate affords veratric acid, $C_9H_{10}O_4$, and an acid $C_{11}H_9O_3N$, accounting for all the carbon atoms of the alkaloid. The acid $C_{11}H_9O_3N$ was first erroneously identified as 7-methoxyquinoline-4-carboxylic acid (29), but the isomerization of galipine to isogalipine clearly requires the presence of a methoxyl group in the 2- or 4-position of the quinoline ring and the acid was subsequently shown to be 4-methoxyquinoline-2-carboxylic acid (26). Galipine may therefore be allotted the structure (XIV). Cusparine differs from galipine only by CH_4 and gives the same acid as does galipine on oxidation; it is therefore allotted the constitution (XV). These structures have been confirmed by the syntheses shown, (XVI) ⟶ (XIV) and (XV), using veratric aldehyde and piperonal, respectively (26,27).

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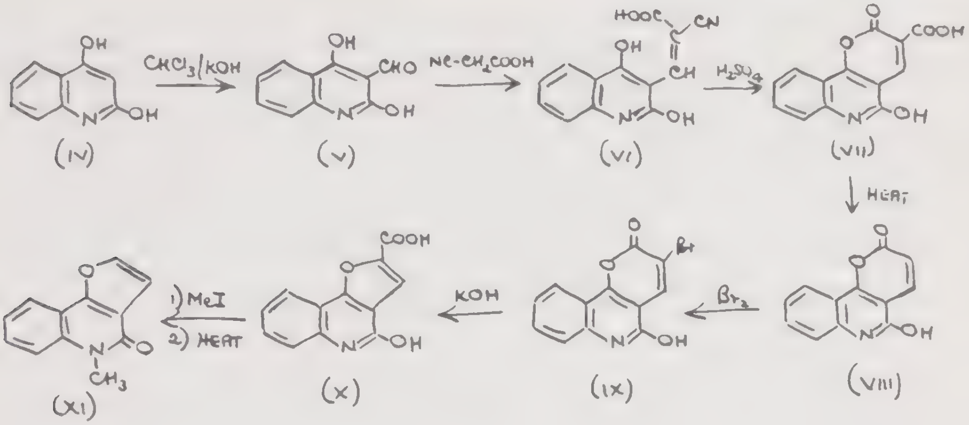
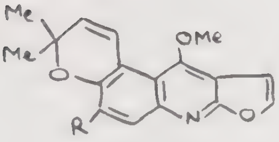
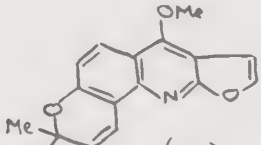
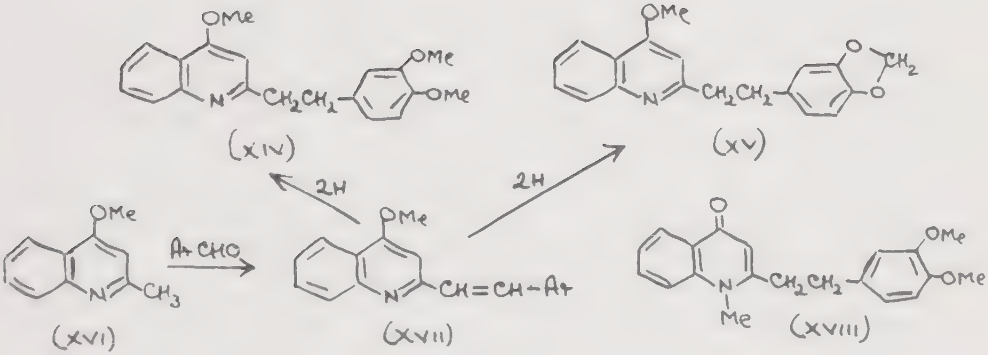
*For total synthesis of dictamine and γ-fagarine see Grundon, M. F. and N. J. McCorkindale, *Chem. & Ind. (London)*, **1956**, 1091.


CHCl3/KOH
NC-CH2COOH
H2SO4
HEAT
Br2
KOH
1) MeI
2) HEAT
(IV)
(V)
(VI)
(VII)
(VIII)
(IX)
(X)
(XI)


(XII)


(XIII)


2H
2H
ArCHO
(XIV)
(XV)
(XVI)
(XVII)
(XVIII)

B. Cuspareine (XIX).

$C_{20}H_{25}O_2N$, contains two —OMe groups and one —NMe— group. On oxidation it affords veratric acid and 2-keto-1-methyl-1,2,3,4-tetrahydroisoquinoline (18). On gentle oxidation with permanganate in acetone it yields isogalipine (XVIII), and accordingly the structure (XIX) was suggested, and was confirmed by the synthesis of cuspareine methyl ether as shown in formulas (XIX) → (XXII) (18).

3. THE CINCHONA ALKALOIDS

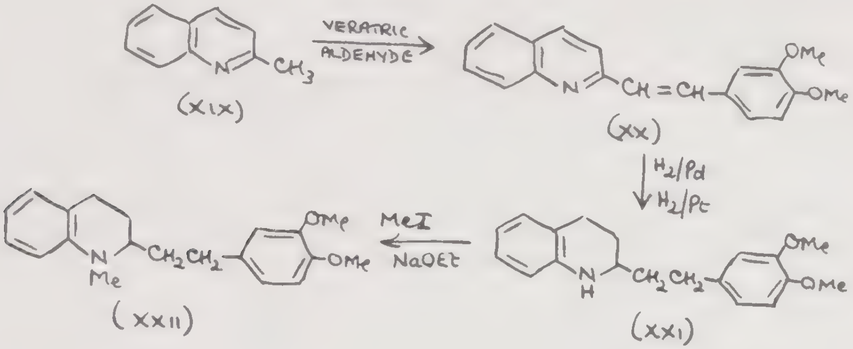
The alkaloids of cinchona bark have long been used medicinally, principally as antimalarials. The two most important are cinchonine and quinine, though more than two dozen alkaloids have been isolated from *Cinchona* and *Remija* species, both of which have been thoroughly investigated.

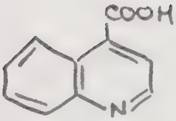
A. Cinchonine (XLII, R = H) and Quinine (XLII, R = OMe).

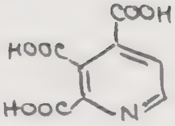
These alkaloids have the compositions $C_{19}H_{22}ON_2$ and $C_{20}H_{24}O_2N_2$, respectively. Both contain one alcoholic —OH group and readily form acetyl derivatives and chloro compounds on treatment with acetic anhydride and phosphorus pentachloride, respectively. Isomers of the alkaloids, conchonidine and quinidine, differing at the alcoholic group are known; oxidation of the stereoisomeric pairs affords the ketones cinchoninone and quininone. The second oxygen atom of quinine is present in a methoxyl group. Both alkaloids contain one double bond, and this is present as a vinyl group, as is shown by the formation of formic acid when the bases are oxidized. The alkaloids both contain one strongly basic and one weakly basic nitrogen atom.

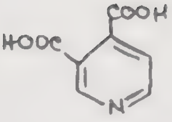
Potash fusion of cinchonine gives quinoline (3) and quinine under the same conditions yields 6-methoxyquinoline (23). The bases lepidine (γ-methylquinoline), β-ethylpyridine, and β-collidine (3-ethyl-4-methylpyridine) are also formed during the potash fusion of cinchonine.

Chromic acid oxidation of cinchonine furnishes cinchoninic acid (XXIII), identified by conversion into the acids (XXIV) and (XXV) (20). Quinine, under the same conditions gives quininic acid,




(XXIII)


(XXIV)


(XXV)

6-methoxycinchoninic acid (XXVI), thus establishing the relationship between the two bases (19,21).

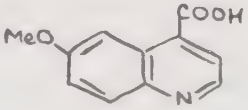
Positive proof of the presence of a quinoline nucleus in these bases was obtained by conversion of the alcohols through the chlorides into the unsaturated bases cinchene and quinene, which on hydrolysis afforded lepidine and 6-methoxy-lepidine, respectively, together with meroquinene. The reaction in the case of cinchene may be represented in the form

$$C_{19}H_{20}N_2 + 2H_2O \longrightarrow C_{10}H_9N + C_9H_{15}O_2N \text{ (meroquinene)}$$

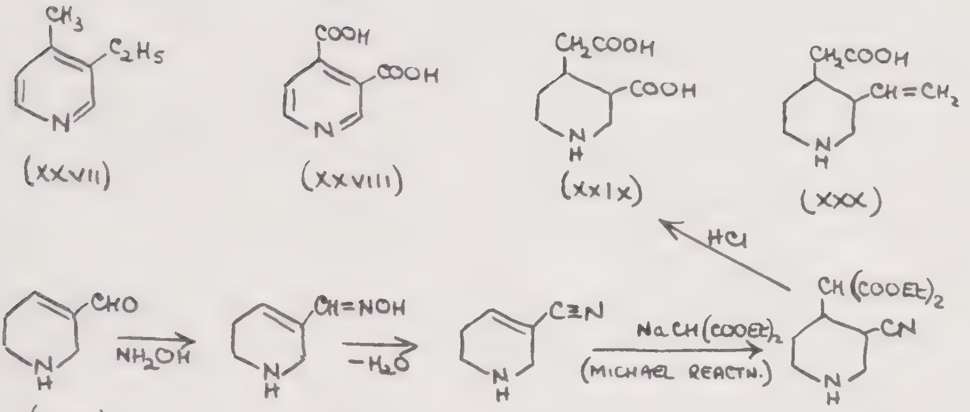
The production of meroquinene (8), also obtained by the direct oxidation (9) of the bases, from both cinchene and quinene shows that the alkaloids differ only in the quinoline portion of the molecule.

Two other substances, cincholoiponic acid $C_8H_{13}O_4N$ (24) and loiponic acid $C_7H_{11}O_4N$ (25), may be isolated from the products of oxidation of cinchonine. Meroquinene, when heated with dilute hydrochloric acid at 240°, is converted smoothly into β-collidine (XXVII), and when oxidized with permanganate is converted into cincholoiponic acid, which is itself further oxidized to loiponic acid. Both these acids contain one —NH— group and two —COOH groups. On the basis of the conversion of meroquinene into β-collidine all these degradation products may be formulated as 3,4-substituted piperidines, and this view was confirmed by the identification of loiponic acid as piperidine-3,4-dicarboxylic acid (XXVIII) (10). Meroquinene and cincholoiponic acid were accordingly formulated as (XXX) and (XXIX), respectively, and the latter was synthesized by the route (XXXI) ⟶ (XXXIV) ⟶ (XXIX) (33).

The mode of linkage of the two parts of the molecule was indicated in the following way; when the alkaloids are boiled with acetic acid the cinchona toxines, cinchotoxine and quinotoxine, are formed, the —CH(OH)— group being converted into —CO—and the strongly basic tertiary nitrogen becoming secondary; these bases may be degraded by acetylation (of the —NH— group), conversion into the isonitroso derivatives, and treatment with phosphorus pentachloride, the products in the case of cinchotoxine being cinchoninyl chloride and acetylmeroquinene nitrile, i.e., (XXXV) ⟶ (XXXVII) and (XXXVIII) (15).

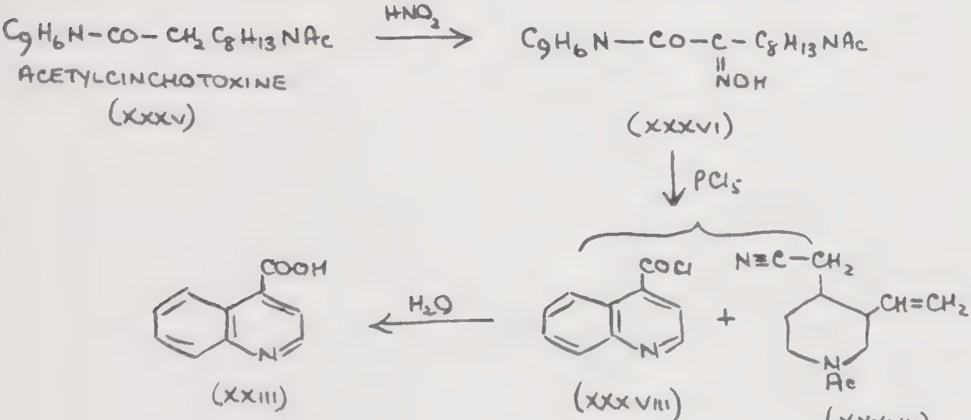


(XXVI)



(XXVII) (XXVIII) (XXIX) (XXX)

(XXXI) (XXXII) (XXXIII) (XXXIV)



$C_9H_6N-CO-CH_2C_8H_{13}NAc$ $\xrightarrow{HNO_2}$ $C_9H_6N-CO-\underset{NOH}{\overset{}{C}}-C_8H_{13}NAc$

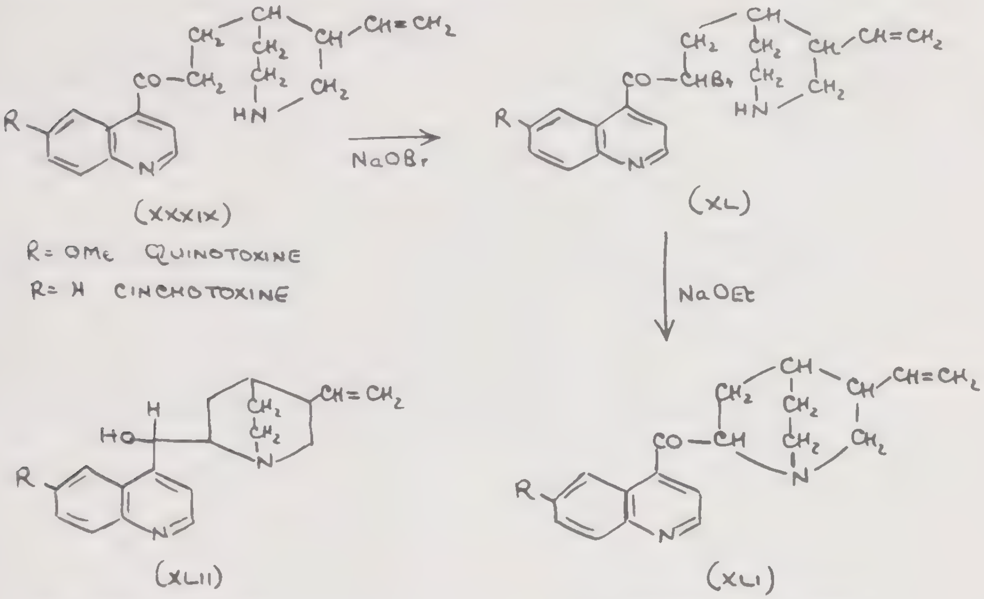
ACETYLCINCHOTOXINE

(XXXV)

(XXXVI)

(XXIII) (XXXVIII) (XXXVII)

The ketone cinchoninone may be split by amyl nitrite to cinchoninic acid and an oximino compound that yields meroquinene on hydrolysis (16). Combining these fragments cinchotoxine may be formulated as (XXXIX, R = H) and quinotoxine as (XXXIX, R = OMe). The toxines may be converted back into cinchonine (XLII, R = H) and quinine (XLII, R = OMe) by bromination at either N or C to give, for example, (XL) followed by treatment with sodium ethoxide and reduction of the resulting cinchoninone (XLI, R = H) and quininone (XLI, R = OMe). In view of this conversion of quinotoxine into quinine any synthesis of the former constitutes a total synthesis of the latter; such a synthesis has been achieved as shown. The ethyl



(XXXIX)

R = OMe QUINOTOXINE
R = H CINCHOTOXINE

(XL)

(XLI)

R = OMe QUININONE
R = H CINCHONINONE

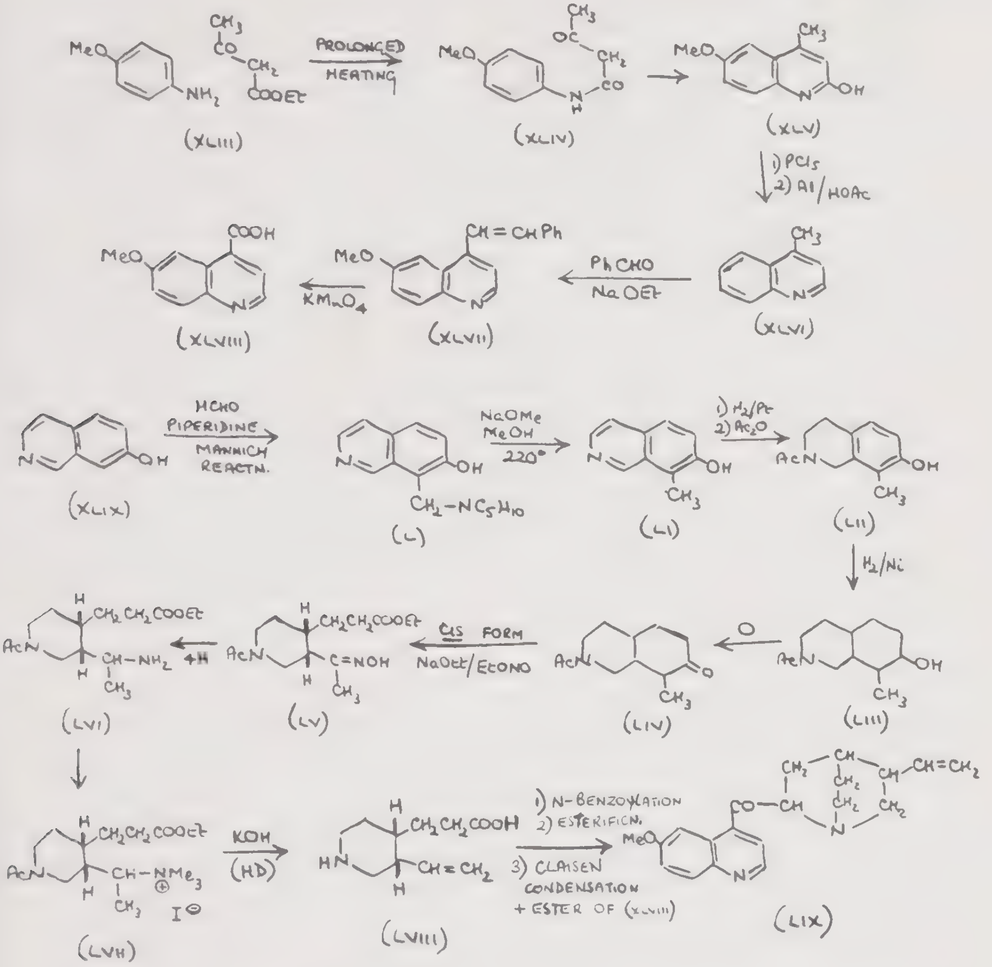
(XLII)

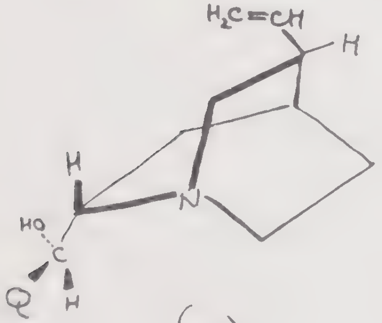
R = OMe QUININE
R = H CINCHONINE

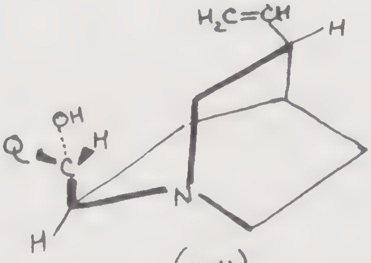
ester of quininic acid (prepared by the process (XLIII) ⟶ (XLVIII) (17)) was condensed with the ethyl ester of (±)-*N*-benzoylhomomeroquinene (prepared by the route (XLIX) ⟶ (LVIII)) and the (±)-quinotoxine so formed resolved. (+)-Quinotoxine prepared in this way was found to be identical with material prepared by the degradation of quinine (34).

The steric arrangement of groups in quinine and cinchonidine (LX) and in cinchonine and quinidine (LXI) shows that quinine and cinchonine belong to two different series (31).

The reactions of the alkaloids are in complete accord with the structures given. An excellent account of the mechanisms of these reactions is given by Turner and Woodward (31) and the salient points may be given here.

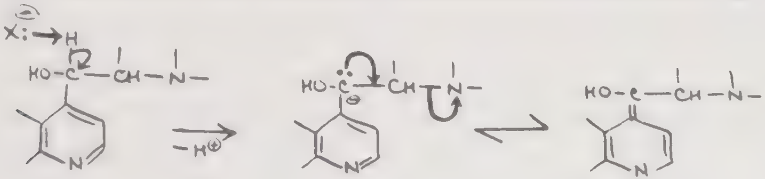

PROLONGED HEATING
(XLIII)
(XLIV)
(XLV)
1) PCl5
2) Al/HOAc
(XLVI)
PhCHO
NaOEt
(XLVII)
KMnO4
(XLVIII)
HCHO
PIPERIDINE
MANNICH REACTN.
(XLIX)
(L)
NaOMe
MeOH
220°
(LI)
1) H2/Pt
2) Ac2O
(LII)
H2/Ni
(LIII)
O
(LIV)
CIS FORM
NaOEt/EtONO
(LV)
+H
(LVI)
(LVII)
KOH
(HD)
(LVIII)
1) N-BENZOYLATION
2) ESTERIFICN.
3) CLAISEN CONDENSATION
+ ESTER OF (XLVIII)
(LIX)


(LX)

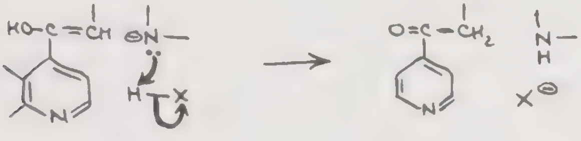

(LXI)

The —CH— group at position 9 of (XLII) is activated in the same way as a —CH_2— group attached to the α- or γ-position of a pyridine ring, $H^{\oplus}$ being easily removed by bases to give the carbanion (LXIII) ⟷ (LXIV). The conversion of quinine into quinotoxine may be represented by the sequence (LXIII) → (LXV) → (LXVI). The process (LXIII) → (LXV) is facilitated by salt formation, which confers a positive charge on the nitrogen atom; in particular the quaternary salts are very easily converted into *N*-alkyltoxines by bases alone (31). In this last process oxides are frequently formed, presumably as shown in (LXVII) → (LXVIII) (31).

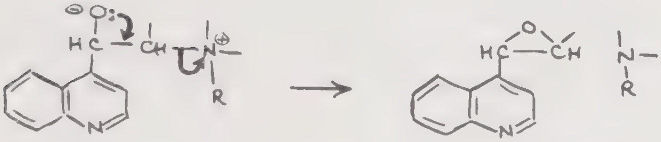
The acid cleavage of the anhydro bases cinchene and quinene (LXIX) to meroquinene and lepidine or 6-methoxylepidine probably proceeds as shown in (LXIX) → (LXXI) + (LXXII); (LXXII), being the lactam of meroquinene, would be expected to be hydrolyzed during the acid cleavage (31). A complex reaction occurs at the same time as this cleavage, the products being apocinchene and



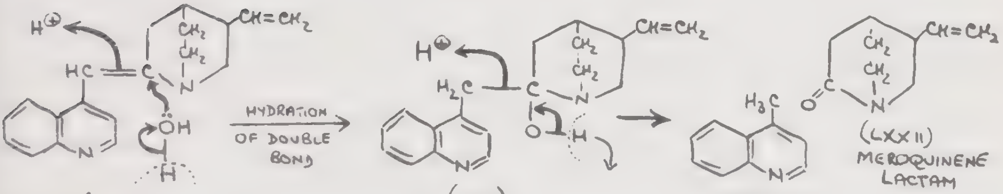
(LXII) (LXIII) (LXIV)



(LXV) (LXVI)



(LXVII) (LXVIII)



(LXIX) ANHYDROBASE

(LXX) CARBINOLAMINE

LEPIDINE (LXXI)

(LXXII) MEROQUINENE LACTAM

apoquinene, (LXXVI, R = H) and (LXXVI, R = OMe), respectively. The course of this change is not clear, but Turner and Woodward suggest some such process as (LXX) ⟶ (LXXIII) ⟶ (LXXVI) (31).

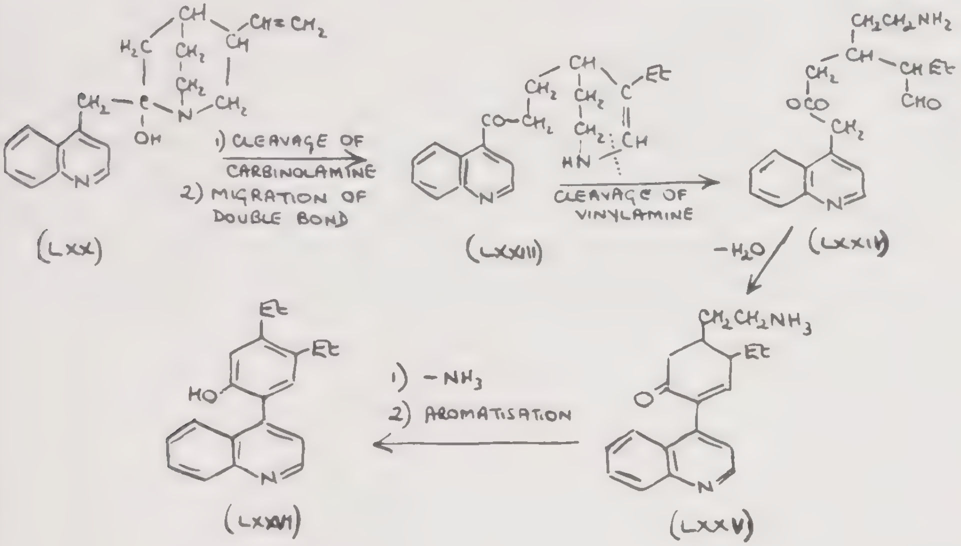
The double bond may be moved by boiling with mineral acids; in some cases, e.g., with cinchonidine, two products are formed (apocinchonidine (LXXVII) and β-cinchonidine (LXXVIII)) (7,12). Addition of hydrogen halides to the vinyl group of quinine followed by treatment with alkali affords the niquine series of bases (LXXIX), C(2) being lost as formaldehyde (22,4). Geometrical isomerism about the double bond is sometimes observed in the niquines.

4. CINCHONAMINE AND QUINAMINE

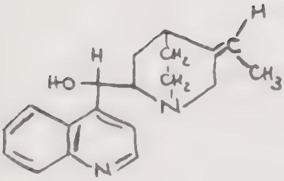
These bases, which contain an indole system instead of a quinoline nucleus, are closely related to the alkaloids of the quinine group and are conveniently discussed at this point.

A. Cinchonamine (LXXXII).

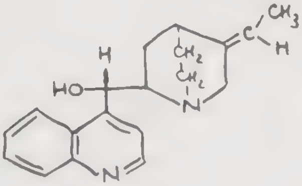
This base has the composition $C_{19}H_{24}ON_2$; it differs from the major cinchona alkaloids in giving, on oxidation, an acid still containing the tricyclic quinuclidine system having the structure (LXXX). The nature of the rest of the molecule was demonstrated by treating the alkaloid with acetic anhydride followed by oxidation of the resulting diacetylallocinchonamine to 2-(β-acetoxyethyl)-indole-1-aldehyde (LXXXI). Cinchonamine may thus be formulated as (LXXXII) and diacetylallocinchonamine as (LXXXIII) (5). Cinchonamine may be smoothly dehydrogenated to dehydrocinchonamine (LXXXIV) (14). Quinuclidine itself may similarly be converted into 4-ethylpyridine.



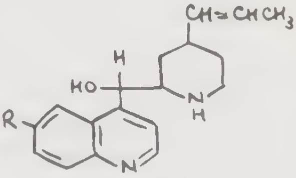
(LXX) (LXXIII) (LXXIV) (LXXV) (LXXVI)



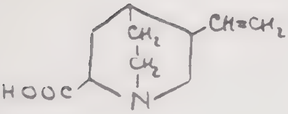
(LXXVII)



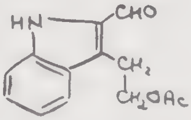
(LXXVIII)



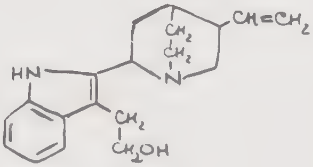
(LXXIX)



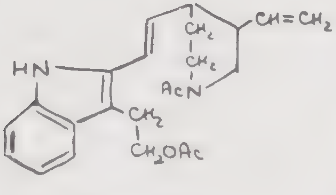
(LXXX)



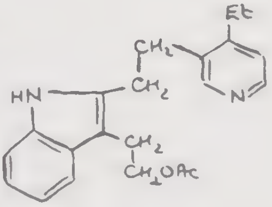
(LXXXI)



(LXXXII)



(LXXXIII)



(LXXXIV)

B. Quinamine (LXXXV).

Another minor alkaloid of cinchona bark is $C_{19}H_{24}O_2N_2$. It also may be oxidized to the acid (LXXX) and was allotted the structure (LXXXV) on the basis of its reduction to cinchonamine by lithium aluminum hydride (5), and its preparation from the latter alkaloid by oxidation with peracetic acid (32), a process that may be represented by the sequence (LXXXVI) ⟶ (LXXXVII) ⟶ (LXXXV) (31).

Acetylapoquinamine (LXXXVIII) is obtained when quinamine is heated with acetic anhydride (6).

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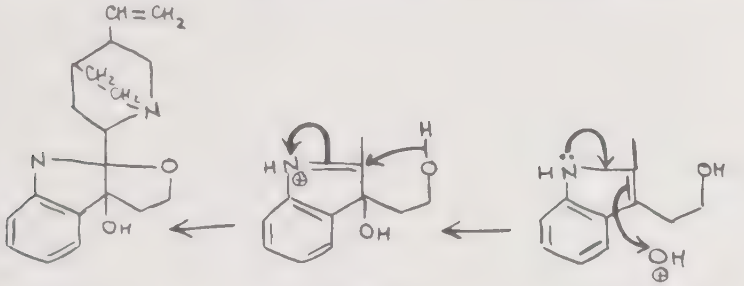
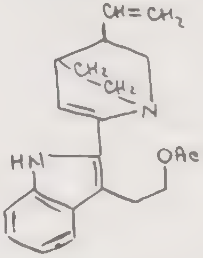


(LXXXV) (LXXXVII) (LXXXVI)



(LXXXVIII)

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CHAPTER 7

ALKALOIDS OF THE INDOLE GROUP: I

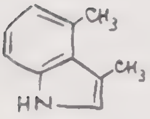
1. THE ERGOT ALKALOIDS

Ergot is a drug obtained from the sclerotium of the fungus *Claviceps purpurea*, and has long been used in medicine on account of its action on the uterus and on the vasomotor center. It consists of a number of alkaloids all of which on hydrolysis afford lysergic acid, which is linked in the alkaloids to a peptide chain.

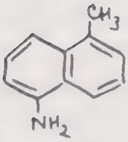
Lysergic Acid (III).

$C_{16}H_{16}O_2N_2$, is an optically active monobasic acid that can be reduced with sodium and amyl alcohol (13) to a dihydro compound. The methyl ester on reduction with sodium and butyl alcohol (Bouveault-Blanc reduction) affords α- and β-dihydrolysergol, $C_{16}H_{20}ON_2$ (14). The acid contains one —NMe— group and active hydrogen determination suggests the presence of a nonbasic —NH—group. Potassium hydroxide fusion of lysergic acid gives 3,4-dimethylindole (I) (17), 1-methyl-5-aminonaphthalene (II), and methylamine (14,15). As methylamine is liberated during this reaction the —NH— group of (I) and the —NH_2 group of (II) must be derived from an indole nucleus in lysergic acid.

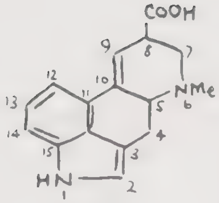
Oxidation of the acid with nitric acid affords a tricarboxylic acid $C_{14}H_9O_8N$ containing one —NMe— group (12), and this on distillation with soda lime yields quinoline. Lysergic acid therefore probably contains a reduced quinoline nucleus. Since the acid contains only one double bond, which according to the ultraviolet spectrum must be conjugated with the indole nucleus, the composition indicates that it must have a tetracyclic structure and the constitution (III) may be advanced for it. The carbonyl group is placed at



(I)



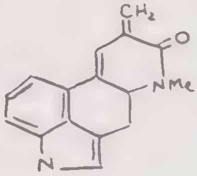
(II)



(III)

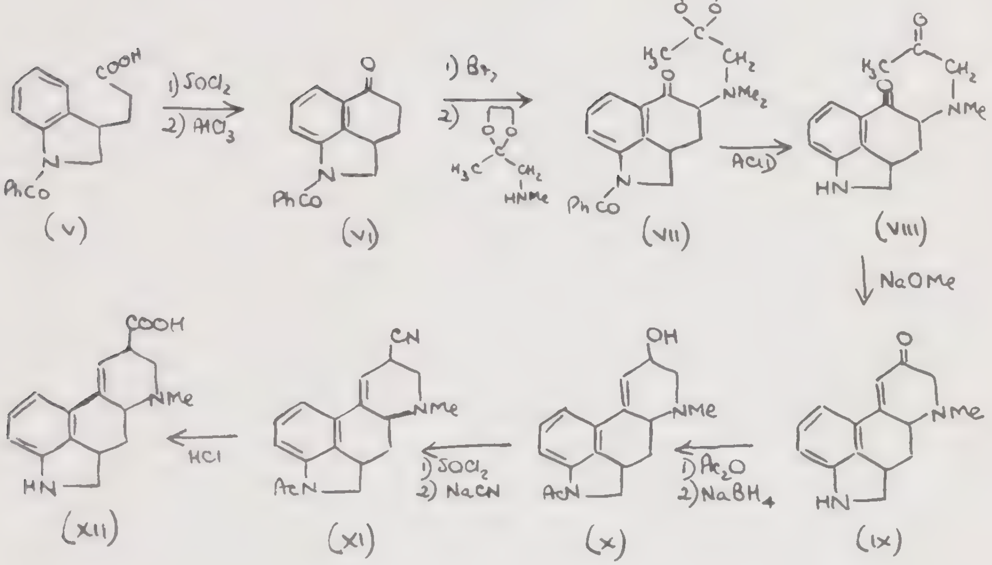
position 8 since lysergic acid behaves like a β-amino acid, giving, on heating, a neutral unsaturated substance (IV) that can be reduced to a tetrahydro compound (44). Dihydrolysergic acid forms a similar lactam (16). The lactam (IV) is optically active, and so must contain an asymmetric carbon atom, and the new double bond is in conjugation with that already present (ultraviolet spectrum). These facts are sufficient to justify the placing of the double bond of lysergic acid at position 9,10 in structure (III). Lysergic acid can be converted into isolysergic acid, a change involving inversion of the —CH—COOH group.

Lysergic acid has been synthesized as shown in (V) → (XII), the last of these intermediates giving (±)-lysergic acid on dehydrogenation (26). The synthetic (±)-lysergic acid has been converted into (±)-isolysergic hydrazide (26), and since the latter has been resolved and converted into ergonovine (ergometrine) (XIII) (7) this constitutes a total synthesis of the alkaloid. Other alkaloids of ergot are ergocristine (XIV, $R = CHMe_2$, $R' = C_6H_5$), ergosine (XIV, $R = Me$, $R' = CHMe_2$), derived from lysergic acid, and ergocristinine and ergosinine with the same structures but derived from isolysergic acid.

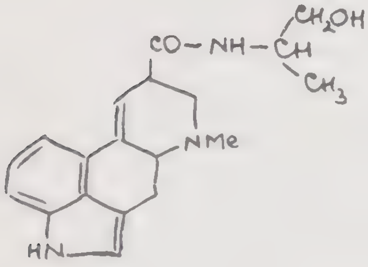


CH2
O
NMe
N

(IV)

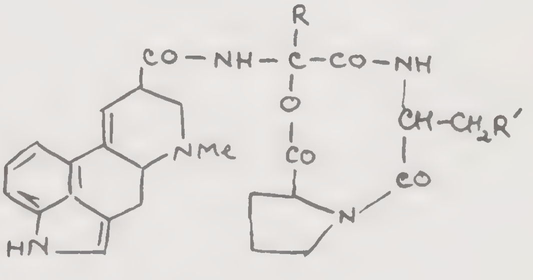


COOH
N
PhCO
(V)
1) SOCl2
2) AlCl3
O
N
PhCO
(VI)
1) Br2
2)
O O
C
H3C CH2
HNMe
O O
C
H3C CH2
O
NMe2
N
PhCO
(VII)
Acid
O
H3C C CH2
O
NMe
HN
(VIII)
NaOMe
O
NMe
HN
(IX)
1) Ac2O
2) NaBH4
OH
NMe
AcN
(X)
1) SOCl2
2) NaCN
CN
NMe
AcN
(XI)
HCl
COOH
NMe
HN
(XII)



CH2OH
CO — NH — CH
CH3
NMe
HN

(XIII)



R
CO — NH — C — CO — NH
O
CO
CH — CH2R′
CO
N
NMe
HN

(XIV)

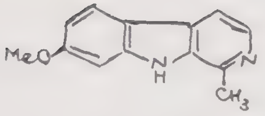
2. THE HARMALA ALKALOIDS (XV), (XVI)

Three alkaloids, harmine, harmaline, and harmalol, occur in the seeds of *Peganum harmala* L. They are closely related and best treated as a group. Harmine has the composition $C_{13}H_{12}ON_2$ and harmaline $C_{13}H_{14}ON_2$. Both are optically inactive. Both may be reduced to tetrahydroharmine (dihydroharmaline) $C_{13}H_{16}ON_2$ (13), and harmaline may be oxidized to harmine (13). Demethylation of harmaline affords the phenol harmalol (14), so the oxygen atom in the alkaloid is present in an —OMe group. Dihydroharmaline forms an *N*-nitroso compound and so must contain an —NH— group (13).

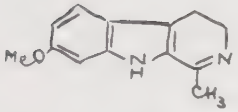
Both harmine and harmaline condense with aldehydes, and in the absence of a carbonyl group this indicates the presence in the molecule of a pyridine ring bearing a methyl group in the α- or γ-position (29). The presence of such a system was confirmed by the oxidation of benzylidene harmine to norharmine-carboxylic acid, $C_{13}H_{10}O_3N_2$, which can be decarboxylated to norharmine, $C_{12}H_{10}ON_2$ (29). The sum of the carbon atoms in the $—CH_3$ and —OMe groups and the benzene and pyridine rings equals the total number present in harmine, suggesting that the second nitrogen atom is present in a pyrrole nucleus. The oxidation of harmine to isonicotinic acid (30) confirms the presence of a pyridine ring and shows that this must be substituted in the γ-position. Harmine may be oxidized to harminic acid, $C_{10}H_8O_4N_2$, which is a vicinal dicarboxylic acid and gives a phthalein on heating with resorcinol (13,29); this corresponds to the oxidation of the benzene ring, which must therefore occupy a terminal position.

The structures (XV), (XVI), and (XVII) for harmine, harmaline, and harminic acid were suggested by Perkin and Robinson (30), the structure for harmaline being based on the optical inactivity of the alkaloid, its formation of addition products with hydroxylamine and hydrogen cyanide, and the quaternary nature of its metho salts.

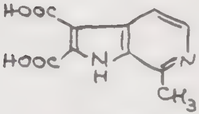
Harmaline and harmine have been synthesized by the routes (XVIII) → (XXI) and (XXII); (XIII) → (XXIV) → (XXI); and (XXV) → (XXVI) → (XXII) (1,10,39).



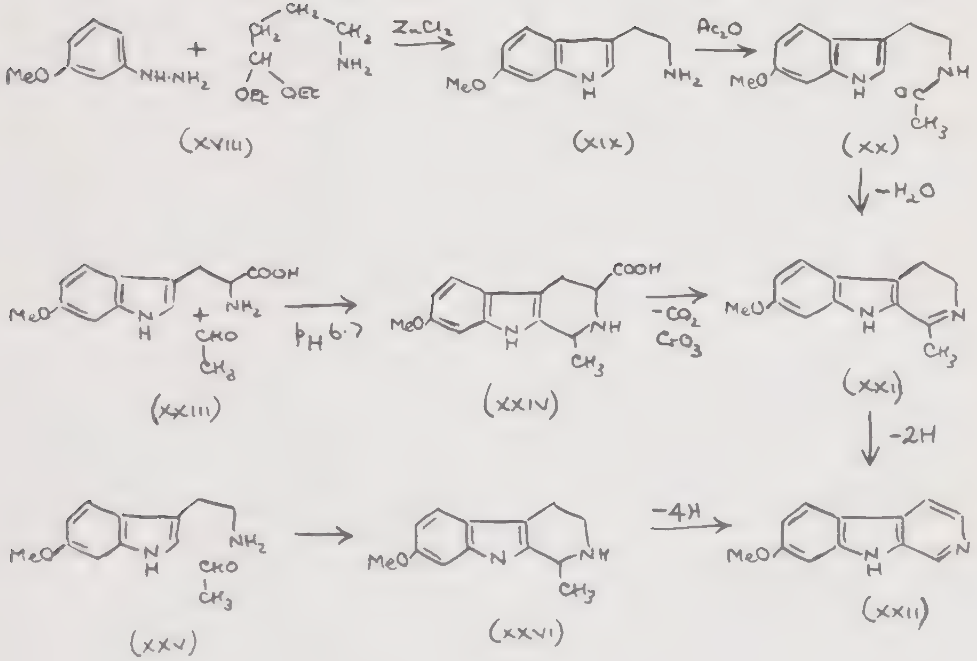
(XV)



(XVI)



(XVII)


(XVIII)
ZnCl2
(XIX)
Ac2O
(XX)
−H2O
(XXIII)
pH 6·7
(XXIV)
−CO2
CrO3
(XXI)
−2H
(XXV)
(XXVI)
−4H
(XXII)

Harmine may be converted into a methiodide (XXVII), readily transformed by loss of hydrogen iodide into the anhydronium base pymethylharmine (XXVIII) (30). Further methylation of (XXVIII) gives the quaternary salt (XXIX), which may be decomposed to indmethylharmine (11).

3. ALKALOIDS OF THE YOHIMBINE GROUP

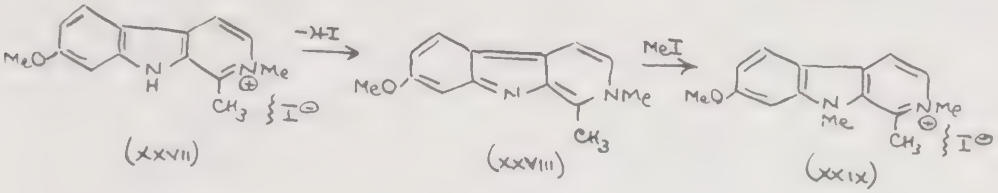
A. Yohimbine (XLI).

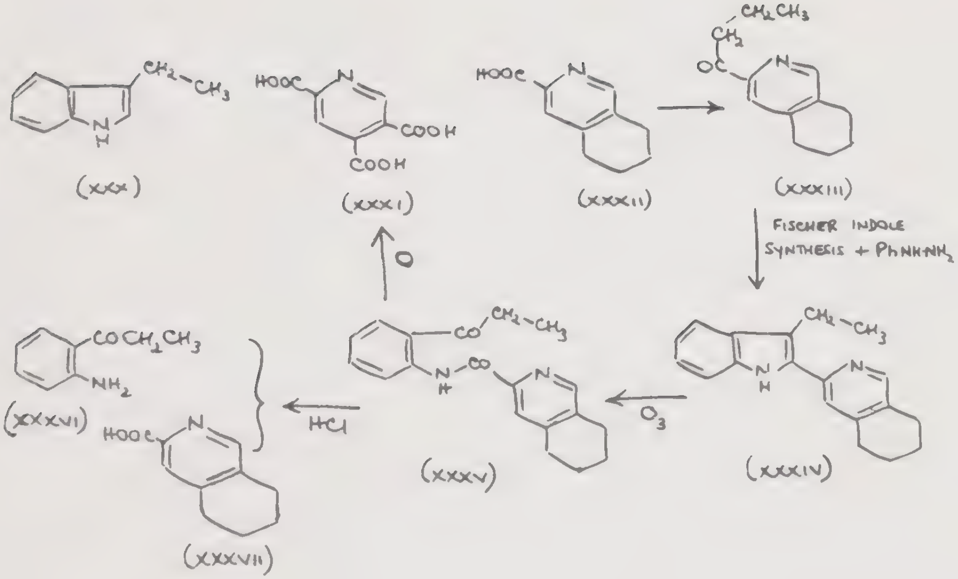
This is the major alkaloid of yohimbe bark, which has frequently been used as an aphrodisiac. It has the composition $C_{21}H_{26}O_3N_2$, and contains one basic nitrogen atom; it forms an acetyl derivative (40) and under certain conditions a diacetyl derivative, indicating the presence of an —OH and probably an —NH— group in the molecule. It may be hydrolyzed by alkalis, when it loses a methyl group, giving yohimbic acid, $C_{20}H_{24}O_3N_2$ (41), and must therefore also contain —COOMe. The presence of —OH and —COOMe may be confirmed by the reduction of yohimbine to yohimbyl alcohol (—COOMe → —CH_2OH) (37) by dehydration of yohimbine to apoyohimbine, and by the decarboxylation of yohimbic acid to yohimbol, $C_{19}H_{24}ON_2$ (9). The base readily gives a methiodide, so the basic nitrogen atom must be tertiary (37).

3-Ethylindole (XXX) and isoquinoline are obtained by the zinc dust distillation of yohimbine (47); selenium dehydrogenation affords yobyrine, $C_{19}H_{16}N_2$, tetrahydroisoyobyrine, $C_{19}H_{20}N_2$, and ketoyobyrine, $C_{20}H_{16}ON_2$ (2,28).

Tetrahydroisoyobyrine may be oxidized with nitric acid to pyridine-2,4,5-tricarboxylic acid (XXXI), and on ozonolysis affords a substance $C_{19}H_{20}O_2N_2$ (XXXV) that on oxidation gives the acid (XXXI) and on hydrolysis yields *o*-aminopropiophenone (XXXVI) and 5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid (XXXVII) (36), and must thus have the structure (XXXIV), confirmed by the synthesis (XXXII) → (XXXIII) → (XXXIV) (22).

Yobyrine gives phthalic acid on oxidation with permanganate, and o-toluic acid on oxidation with chromic acid; it can be condensed with aldehydes, suggesting the presence of a pyridine ring with a —CH_2— substituent adjacent to the nitrogen (48). These reac-

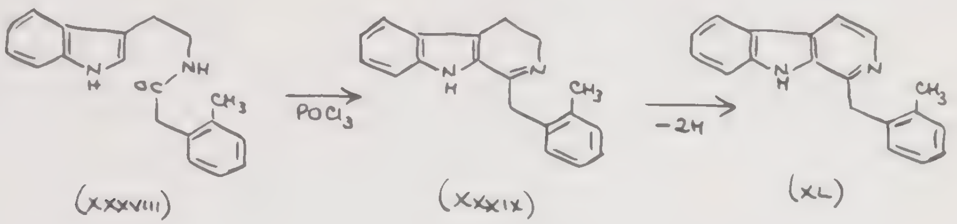

MeO
N
H
N Me
⊕
CH₃
I⊖
(XXVII)
−HI
MeO
N
NMe
CH₃
(XXVIII)
MeI
MeO
N
Me
N Me
⊕
CH₃
I⊖
(XXIX)


CH₂−CH₃
N
H
(XXX)
HOOC
N
COOH
COOH
(XXXI)
HOOC
N
(XXXII)
CH₂CH₃
CH₂
OC
N
(XXXIII)
FISCHER INDOLE SYNTHESIS + PhNH·NH₂
CH₂−CH₃
N
H
N
(XXXIV)
O₃
CO
CH₂−CH₃
N
H
CO
N
(XXXV)
O
HCl
COCH₂CH₃
NH₂
(XXXVI)
HOOC
N
(XXXVII)

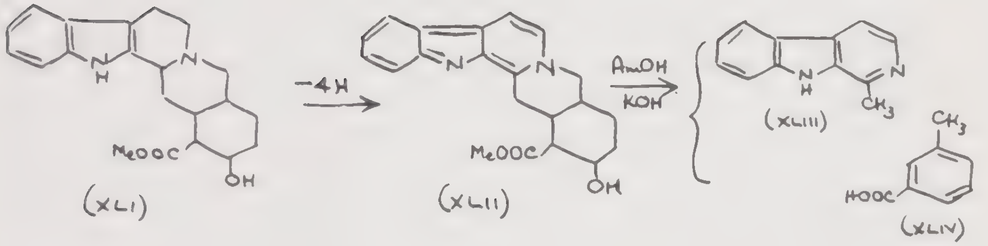
tions are satisfactorily accounted for by the structure (XL), which was confirmed by the synthesis of yobyrine by the route (XXXVII) → (XL) (5).

From these results it was concluded that the nuclear structure of yohimbine (which is fully hydrogenated except for the indole system) is represented by (XLI). The position of the —COOMe group was deduced as follows. Dehydrogenation of yohimbine affords tetradehydroyohimbine (XLII), which on boiling with amyl alcoholic potash is decomposed to harman (XLIII) and *m*-toluic acid (XLIV) (38). The elucidation of the structure of ketoyobyrine (see below) provides support for this location of the —COOMe group. Ketoyobyrine (XLVI) and yobyrine (XL) are believed to be formed through the intermediate (XLV), ketoyobyrine by amide formation and loss of 2H, yobyrine by decarboxylation and loss of 4H.

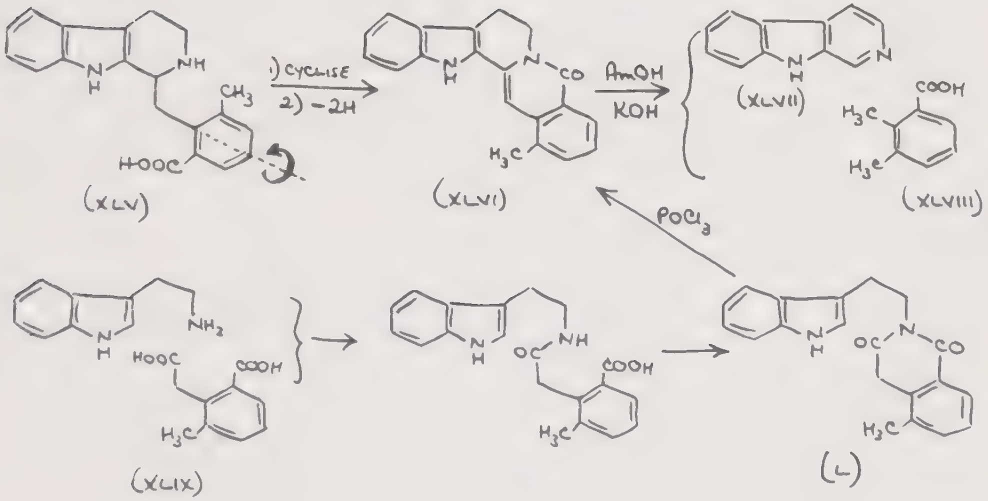
Ketoyobyrine. Some indication of the nature of the structure of ketoyobyrine is given by the alkaline degradation of this nonbasic substance to norharman (XLVII) and 2,3-dimethylbenzoic acid (XLVIII) on heating with amyl alcoholic potash (2). It has been synthesized by the processes shown in formulas (XLIX) → (L) → (XLVI) (6,23,35).



NH
H
OC
CH3
POCl3
(XXXVIII)
N
H
N
CH3
(XXXIX)
−2H
N
H
N
CH3
(XL)



N
H
N
MeOOC
OH
(XLI)
−4H
N
N
MeOOC
OH
(XLII)
AmOH
KOH
N
H
N
CH3
(XLIII)
CH3
HOOC
(XLIV)



N
H
NH
CH3
HOOC
(XLV)
1) CYCLISE
2) −2H
N
H
N
CO
H3C
(XLVI)
AmOH
KOH
N
H
N
(XLVII)
COOH
H3C
H3C
(XLVIII)
POCl3
N
H
NH2
HOOC
COOH
H3C
(XLIX)
N
H
OC
NH
COOH
H3C
N
H
OC
N
CO
H3C
(L)

The position of the —OH group in yohimbine was demonstrated by the results of Oppenauer oxidation, which gives the ketone yohimbone (LI) (—CH(OH)— → —CO)) which no longer contains —COOMe or —COOH; this indicates that the first product of the oxidation is a β-keto ester which, under the alkaline conditions of the reaction, is hydrolyzed and decarboxylated (48).

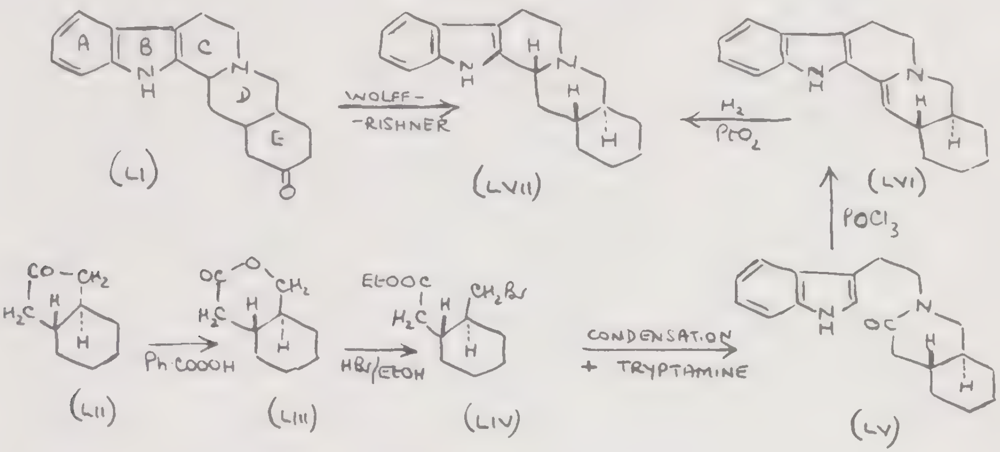
Wolff-Kishner reduction of yohimbone affords yohimbane (LVII), in which three of the original five asymmetric centers of yohimbine remain (19). In this base and therefore in yohimbine rings D and E are, according to Witkop (49), *trans* fused, a view confirmed by the synthesis of (±)-yohimbane by the route (LII) ⟶ (LVII) from (±)-*trans*-hydrinan-2-one (46). The corresponding *cis*-D/E substance, (±)-alloyohimbane, has been prepared in the same way from (±)-*cis*-hydrindan-2-one (45); in this synthesis the reduction of the vinylamine, *cis*-(LVI), with sodium and liquid ammonia gave (±)-3-epi-alloyohimbane, differing from (±)-alloyohimbane in the configuration of the asymmetric center at position 3 (45).

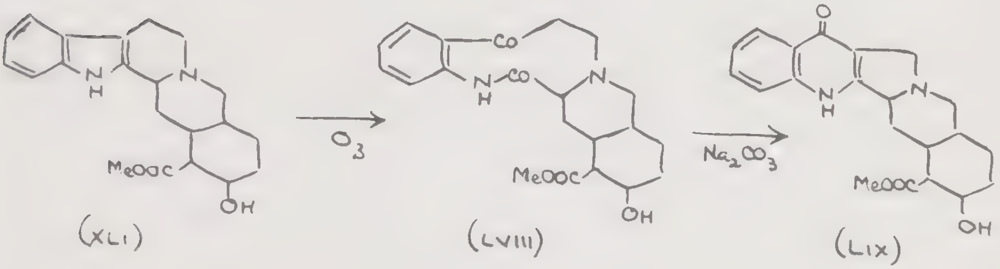
The ozonolysis of yohimbine yields the amide (LVIII), which cyclizes to the base (LIX) under alkaline conditions (50).

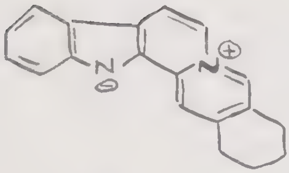
Isomers of yohimbine, namely β-, γ-, δ-, iso-, allo-, and pseudoyohimbine and yohimbene have been isolated from natural sources; they appear to differ at one or more of the asymmetric centers, see Marion (27). Stereochemistry of alkaloids has been studied by Janot (18).

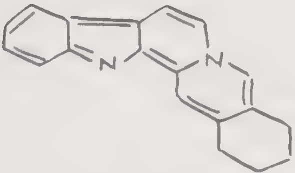
B. Sempervirine (LXI)–(LX).

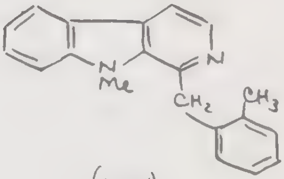
This is one of the alkaloids of *Gelsemium sempervirens*; it has the composition $C_{19}H_{16}N_2$. When heated with selenium it yields yobyrine (XL) and when heated with Raney nickel in xylene it gives tetrahydroisoyobyrine (XXXIV) (8,33). Sempervirine is optically inactive and orange in color; the structure (LX) resonating with (LXI) satisfactorily accounts for the properties of the alkaloid, particularly the absence of —NH— bands in the infrared spectrum (51). This structure was confirmed by the synthesis of sempervirine methochloride (LXIV) by the condensation of the lithium derivative of *N*-methylharman (LXII) with 2-isopropoxymethylenecyclohexanone (LXXIII) (31). When the methochloride (LXIV) is heated it is converted into ind-*N*-methylyobyrine (LXV) (51).

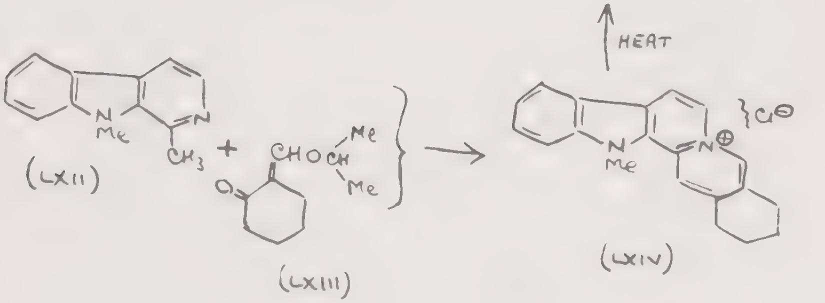

A
B
C
D
E
(LI)
WOLFF-
-KISHNER
(LVII)
H_2
PtO_2
(LVI)
$POCl_3$
(LII)
Ph·COOOH
(LIII)
EtOOC
CH_2Br
HBr/EtOH
(LIV)
CONDENSATION
+ TRYPTAMINE
(LV)


MeOOC
OH
(XLI)
O_3
(LVIII)
Na_2CO_3
(LIX)


(LX)


(LXI)


(LXV)


HEAT
(LXII)
+
CHOCH
Me
Me
(LXIII)
Cl⊖
(LXIV)

4. THE PHYSOSTIGMINE GROUP

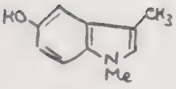
A. Physostigmine (LXVIII, R = CO · NHMe).

This alkaloid, also known as eserine, is the main alkaloid present in the seeds of the Calabar bean (*Physostigma venenosum*). It is important medicinally as it produces miosis when instilled into the eye. It has the composition $C_{15}H_{21}O_2N_3$, and one of the nitrogen atoms is present in the system $CH_3NH—CO—O—$ since the alkaloid gives methylurethane, $CH_3NH—CO—OEt$, when heated with sodium ethoxide in the absence of air, and methyl isocyanate $CH_3N{=}C{=}O$ when oxidized (31).

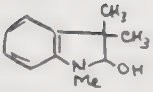
The second product of hydrolysis is a phenolic base, eseroline, the ethyl ether of which has been named eserethole. Pyrolysis of eseroline methiodide yields physostigmol, $C_{10}H_{11}ON$, shown by synthesis to be 5-hydroxy-1,3-dimethylindole (LXVI) (42). The presence of a dihydro-indole system in physostigmine is indicated by the feeble basicity of one of the nitrogen atoms, and by the ultraviolet spectrum of the base (4).

Eserethole methiodide on heating with potassium hydroxide affords eseretholemethine, which is a pseudo base and can be converted back into eserethole methiodide by treatment with hydriodic acid (3,32). This methine resembles 1,3,3-trimethyl-2-indolinol (LXVII), and like this can be oxidized by ammoniacal silver nitrate ($—CH(OH)— \rightarrow —CO—$), and probably has a similar structure. The expansion of (LXVI) to the structure of eseroline must involve the addition of one more ring, containing C_3H_7 and a tertiary nitrogen, to give a structure that may easily be converted into a substance similar to (LXVII). This is most satisfactorily achieved as shown in (LXVIII, R = H), the angular methyl group being very probably present in eseroline since physostigmol (LXVI) is obtained in 60% yield during the pyrolysis of the methiodide, making the alternative structure (LXIX) most unlikely (43).

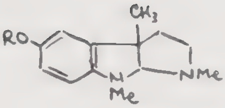
Eserethole methiodide then becomes (LXX) and eseretholemethine (LXXI). The reduction of eserethole catalytically or with zinc dust and hydrochloric acid proceeds with the addition of two atoms of hydrogen and the production of dihydroeserethole, which is a secondary amine (LXXII), generated by reductive scission of the termi-



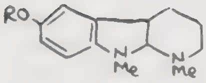
(LXVI)



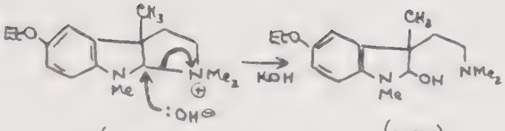
(LXVII)



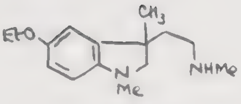
(LXVIII)



(LXIX)



(LXX) (LXXI)



(LXXII)

nal ring (43). Physostigmine itself may thus be represented by the formula (LXVIII, R = CO • NHMe).

Eserethole (LXXVIII) has been synthesized by several methods (24,25,34) but the most satisfactory process is that shown in formulas (LXXIII) → (LXXIX) (20). The resulting (±)-base can be resolved, and the *levo*-form is identical with eserethole prepared from physostigmine (21). Since eserethole can be de-ethylated to eseroline (LXXVIII, R = H) and the latter can be converted into physostigmine by treatment with methyl isocyanate, the syntheses of eserethole can be regarded as total syntheses of physostigmine.

The alkaloids *Quinamine* and *Cinchonamine*, which are derivatives of indole, are discussed in Chapter 6.

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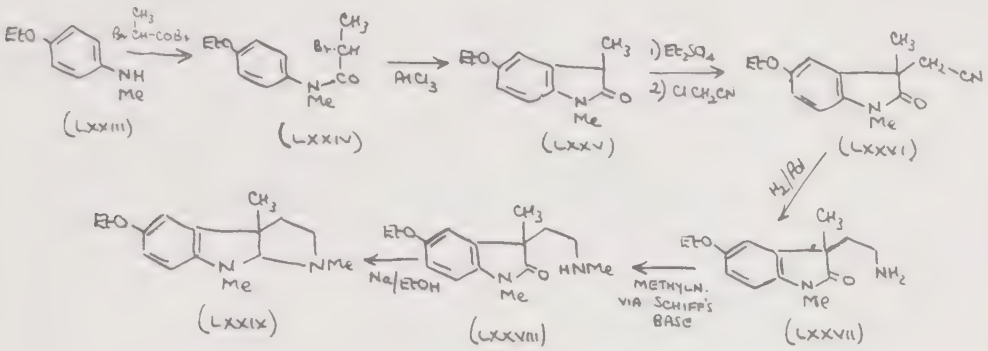

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CHAPTER 8

ALKALOIDS OF THE INDOLE GROUP: II

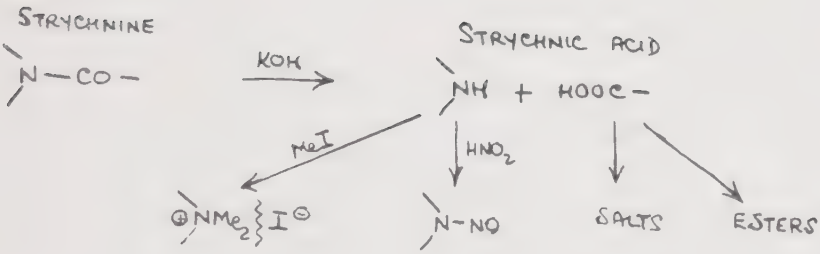
STRYCHNOS ALKALOIDS

A. Strychnine (LXI) and Brucine.

These two alkaloids, which have the compositions $C_{21}H_{22}O_2N_2$ (9) and $C_{23}H_{26}O_4N_2$, respectively, are obtained from the seeds of *Strychnos nux vomica*, together with the bases α- and β-colubrine, $C_{22}H_{24}O_3N_2$. The elucidation of the structure of and the synthesis of strychnine was probably the last great problem in organic chemistry to be solved wholly by means of the traditional methods.

Strychnine is a strong, monoacid tertiary base containing no —NMe— group. The second nitrogen atom is nonbasic and was soon recognized as being part of an amide system; this was confirmed by warming the base with potassium hydroxide solution, when hydrolysis of the amide occurred, the product being strychnic acid (40). This acid contains an —NH— group, as it forms an *N*-nitroso compound on treatment with nitrous acid, and gives *N*-methylstrychnic acid methiodide on treatment with methyl iodide; it also contains a —COOH group as it readily forms salts, and can be induced to form esters.

Strychnine may therefore be represented as $C_{20}H_{22}O\overset{(b)}{N}\text{—}(\overset{(a)}{N}\text{—}CO\text{—})$ and strychnic acid as $C_{20}H_{22}O\overset{(b)}{N}\text{—}(\text{—}\overset{(a)}{N}H\text{—})(\text{—}COOH)$. When strychnine is heated with water at 160–180°, or better with methanolic ammonia, it is converted into isostrychnine which, unlike strychnine, contains a hydroxyl group (4). Isostrychnine may be hydrolyzed to isostrychnic acid (4).


STRYCHNINE
N—CO—
KOH
STRYCHNIC ACID
NH + HOOC—
MeI
HNO2
⊕NMe2 I⊖
N-NO
SALTS
ESTERS

The second oxygen atom of strychnine is inert to the usual reagents, and probably is present in an ether link; this must be a cyclic ether as the oxygen atom remains firmly in the molecule during most degradations. It can, however, be removed by reduction with hydriodic acid and red phosphorus when desoxystrychnine, $C_{21}H_{24}ON_2$, is obtained. This base still contains the amide system and can be hydrolyzed to desoxystrychnic acid.

Strychnine contains one double bond and can be catalytically hydrogenated to dihydrostrychnine. The amide group can also be reduced, electrolytically, to $—N—CH_2—$, to give strychnidine, $C_{21}H_{24}ON_2$ (41), and to $—NH— + HO—CH_2—$; the product of this stage of reduction, tetrahydrostrychnine, may be dehydrated to strychnidine. Both strychnidine and tetrahydrostrychnine may be further reduced at the double bond. These reductions are summarized below.

$$\begin{tikzcd}
\text{strychnidine} \arrow[r, "Pd/H_2"] & \text{dihydrostrychnidine} \\
\text{strychnine} \arrow[u, "ER"'] \arrow[r, "Pd/H_2"] \arrow[d, "ER"] & \text{dihydrostrychnine} \arrow[u, "ER"'] \arrow[d, "ER"] \\
\text{tetrahydrostrychnine} \arrow[r, "Pd/H_2"] & \text{hexahydrostrychnine}
\end{tikzcd}$$

Desoxystrychnine can also be reduced at the amide group to give strychnoline (desoxystrychnidine), $C_{21}H_{26}N_2$ (38).

Strychnine and some of its simple derivatives, but not strychnidine, condense with benzaldehyde readily in alcoholic potassium hydroxide, giving benzylidinestrychnine and its derivatives (32). Strychnine therefore contains a reactive methylene group, and, since this cannot be activated by the oxygen atom of the ether group, and in view of the failure of strychnidine to undergo such a condensation, this methylene group must be activated by the amide carbonyl group. Strychnine must therefore contain the system $—N—CO—CH_2—$. (Compare the condensation of oxindole with benzaldehyde.)

The relationship of strychnine to strychnidine is that of an acylated alkylaniline to an alkylaniline. Thus strychnine can be sulfonated, halogenated, and nitrated. However, it does *not* couple

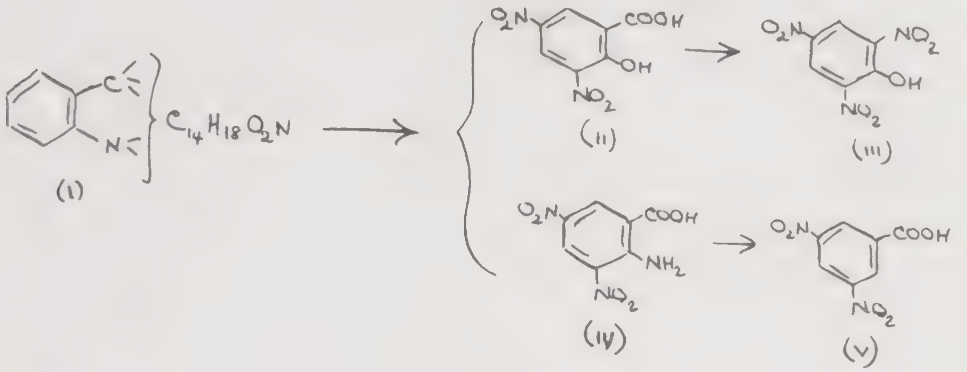
with diazonium salts and is *not* oxidized by ferric salts in weakly acid solutions, whereas strychnidine is readily oxidized by ferric salts and can be coupled with diazotized sulfanilic acid to give an azo compound resembling methyl orange in indicator properties, and this can be reduced to aminostrychnidine which is similar to *p*-aminodimethylaniline and will give rise to analogs of toluylene blue and toluylene red (21,26,31,33). Moreover benzaldehyde can be condensed with strychnic acid methyl ester to give a dyestuff analogous to malachite green.

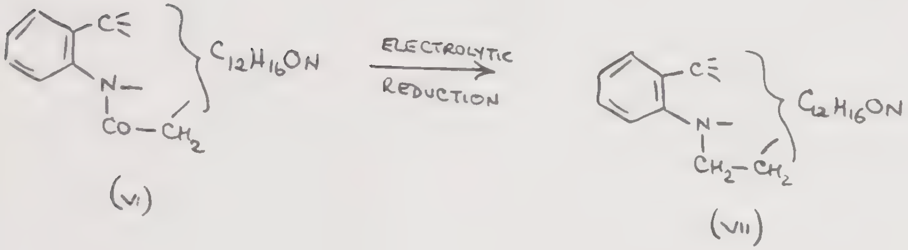
When strychnine is heated with dilute nitric acid, picric acid (37) and 3,5-dinitrobenzoic acid (30) are obtained, and these fairly clearly owe their formation to processes of the type (I) ⟶ (II), (III), (IV), and (V) (35). Accordingly we can write the transformation of strychnine into strychnidine in the form (VI) ⟶ (VII).

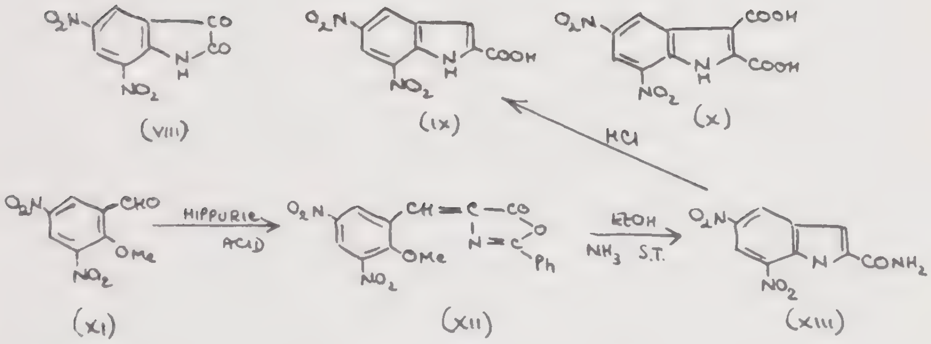
When treated with concentrated nitric acid strychnine gives dinitrostrychol carboxylic acid (41), which may be decarboxylated to dinitrostrychol. Dinitrostrychol is still an acid and can be converted into an amide which can be transformed via the amine (Hofmann degradation) to dinitroisatin (VIII) (29). Dinitrostrychol may thus be allotted the structure (IX) and this was proved by the synthesis of the corresponding amide, (XI) ⟶ (XIII) (14). Dinitrostrychol, which may also be converted into dinitroisatin, thus has the structure (X). This was an important conclusion as for a time dinitrostrychol was thought to be a dinitrodihydroxyquinoline and dinitrostrychol carboxylic acid to be a monocarboxylic acid.

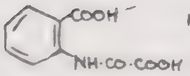
Oxidation of strychnine with alkaline permanganate affords the acid (XIV), whereas brucine under the same conditions affords the acid (XV) (39). The relationship of the two alkaloids is thus made clear, brucine being dimethoxystrychnine; as both alkaloids must contain an indole nucleus we can write strychnine as (XVI) and brucine as (XVII).

The benzene nucleus of brucine can be destroyed by oxidation to furnish a variety of products as follows. Oxidation of brucine with chromic acid affords bruciquinone (XIX) (28), which on oxidation with nitric acid is converted into cacothelin, $C_{21}H_{21}O_7N_3$ (XX) (18); this in turn with bromine is oxidized to an acid $C_{19}H_{22}O_6N_2$ (XXI) which with chromic acid is oxidized to an acid $C_{16}H_{20}O_4N_2$ (XXIII) (13),

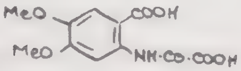




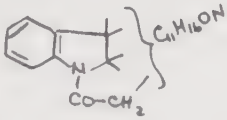




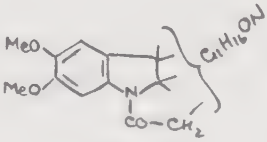
(XIV)



(XV)



(XVI)



(XVII)

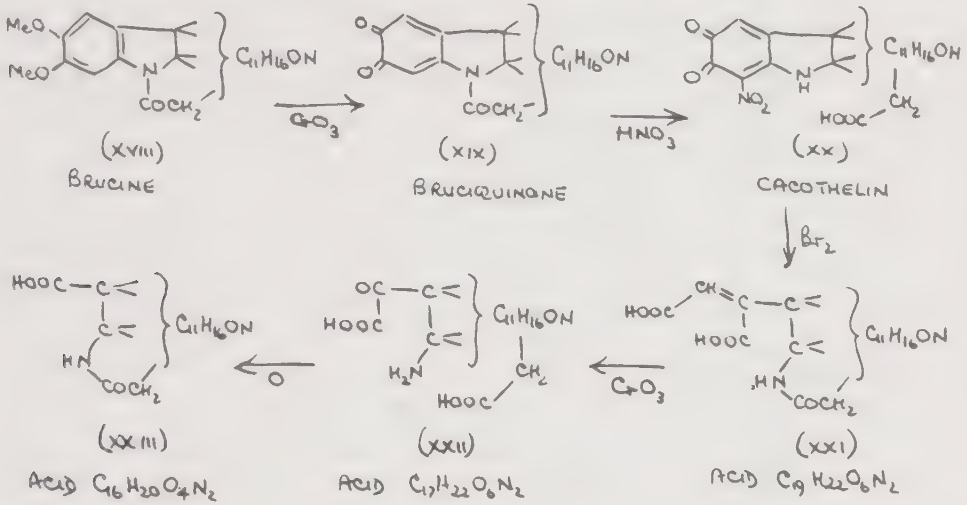
also obtainable by the chromic acid oxidation of brucine and strychnine. An intermediate acid, $C_{17}H_{22}O_6N_2$ (XXII), has also been isolated (12).

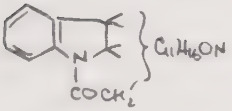
It was suggested some time ago by Leuchs (25) that such substances, in which the aromatic nucleus has been destroyed, be named as derivatives of the hypothetical bases nucine and nucidine, related to strychnine and strychnidine as shown in formulas (XXIV) → (XXVII). The following examples may be given. Strychnidine is oxidized by chromic acid to 2,3-diketonucidine (XXVIII), which may be reduced to 2-keto-3-hydroxynucidine (XXIX) and oxidized to carboxyaponucidine (XXX).

The two carboxyl groups present in dinitrostrychol carboxylic acid (X) represent the remnants of the rest of the molecule, and are probably derived from a six-membered ring. When strychnine is treated with 80% sulfuric acid and a crystal of potassium dichromate a deep purple color is produced. This, the Otto reaction, is characteristic of the —N—CO— group and is not given by strychnidine. Certain substituted indole and quinoline derivatives give very similar results (e.g., the amide (XXXI) gives the Otto reaction whereas the base (XXXII) does not), but the color obtained with strychnine is most closely matched by that given by certain derivatives of hydrogenated carbazoles, indicating that strychnine probably contains the system (XXXIII). This is supported by the fact that carbazole and indole are produced when strychnine is distilled with lime (11).

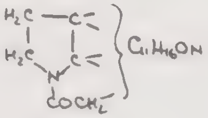
Knowledge of the rest of the structure of the molecule is mainly the result of exhaustive studies of the oxidation of strychnine and brucine. Oxidation of strychnine with permanganate in acetone affords strychninonic acid, $C_{21}H_{20}O_6N_2$, which is a keto-monocarboxylic acid containing no double bond (16,22). This acid shows no basic properties, both nitrogen atoms being present in —N—CO— groups; this is demonstrated by the production of a tricarboxylic acid $C_{21}H_{24}O_8N_2$, with the addition of two molecules of water on hydrolysis. The "ether oxygen" atom of strychnine is still present in strychninonic acid.

Reduction of strychninonic acid with sodium amalgam yields strychninolic acid, $C_{21}H_{22}O_6N_2$, which is no longer ketonic; it forms

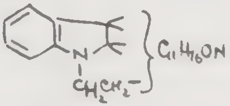




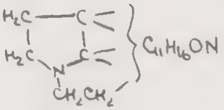
(XXIV)
STRYCHNINE



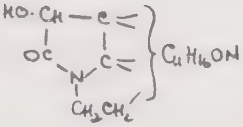
(XXV)
NUCINE



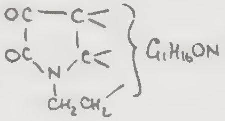
(XXVI)
STRYCHNIDINE



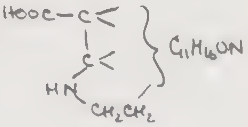
(XXVII)
NUCIDINE



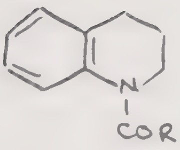
(XXVIII)



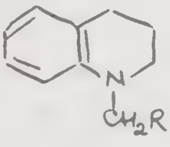
(XXIX)



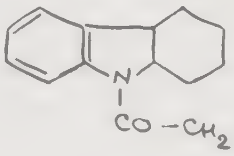
(XXX)



(XXXI)



(XXXII)



(XXXIII)

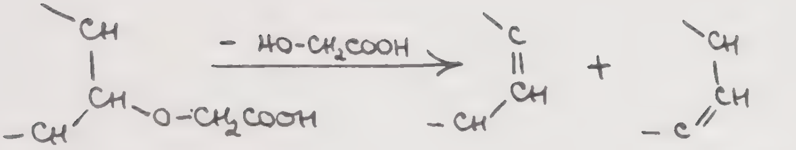
an acetyl derivative and is evidently the product of reduction of —CO— to —CH(OH)—. Dihydrostrychninonic acid, epimeric with strychninolic acid at the —CH(OH)— group, can be isolated from the products of oxidation of strychnine (22,23).

When strychninolic acid is allowed to stand for several hours with *normal* aqueous sodium hydroxide decomposition occurs *without* hydrolysis of the amide groups, and strychninolone, $C_{19}H_{18}O_3N_2$, is produced together with glycollic acid, HO—CH_2—COOH (23, 24). Strychninolone does not retain the "ether oxygen" atom of strychnine. It contains three oxygen atoms, present in two amide groups and one —CH(OH)— group (it forms an acetyl derivative and can be hydrolyzed to a diamino-dicarboxylic acid). It exists in two forms, strychninolone-*a* and strychninolone-*b*, which differ in the position of a double bond.

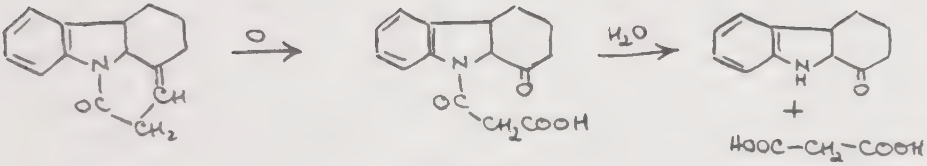
The degradation of brucine follows the same course, giving brucinonic acid, brucinolic acid, and brucinolone (16,24,27).

The formation of strychninolone from strychninolic acid involves the loss of the carboxyl group present in the latter and, as this appears as glycollic acid, strychninolic acid must contain the system (XXXIV) and strychninolone-*a* and -*b* the systems (XXXV) and (XXXVI), and to provide a driving force for the reaction the —O—CH_2—COOH group must be in the β-position to a carbonyl group. Attachment of the —O—CH_2—COOH group in the α-position to the —CO— is impossible as a —CH_2— group must be adjacent to the —CO— to account for the production of benzylidine derivatives of strychnine and brucine, and attachment of the —O—CH_2—COOH group in the γ-position is unlikely as strychninolone-*a*, which is the major product of the elimination of glycollic acid, is an α,β-unsaturated amide.

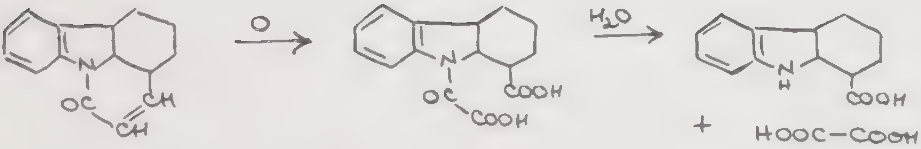
The two isomers strychninolone-*a* and strychninolone-*b* can be further oxidized to malonic acid and oxalic acid, respectively (20), and must therefore contain the systems (XXXVII) and (XL), respectively. The double bonds present in these compounds are produced by the loss of glycollic acid from strychninolic acid, which must therefore have the part-structure (XLIII), and as the —COOH group of this acid is clearly derived from a double bond in strychnine, the alkaloid must contain the part-structure (XLIV).



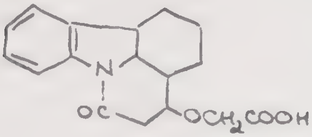
(XXXIV) (XXXV) (XXXVI)



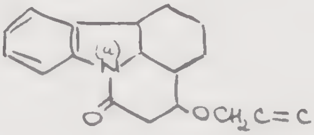
(XXXVII) (XXXVIII) (XXXIX)



(XL) (XLI) (XLII)



(XLIII)

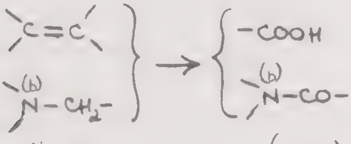


(XLIV)

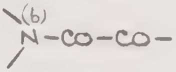
In the formation of strychninonic acid from strychnine the process (XLV) ⟶ (XLVI) occurs, where —N(b)— is the basic nitrogen atom of the alkaloid. The product (XLV) behaves as an α-ketoamide, and must therefore contain the system (XLVII) and, as it is not an aldehyde, (XLVII) can be expanded to (XLVIII). Therefore strychnine must contain the arrangement (XLIX), the presence of which is supported by the formation of dihydrostrychninonic acid during the permanganate oxidation of the alkaloid. This process must proceed as shown in formulas (L) ⟶ (LI), followed by hydrolytic fission. In accordance with experience this would be an improbable reaction unless the system were (LII), and since the —CO— attached to the indole nitrogen atom in strychnine is also linked to —CH_2— the system (LII) can be expanded to (LIII). Strychnine is accordingly seen to contain the part-structure (LIV).

The alkaloid can be oxidized by air, ozone, or hydrogen peroxide to pseudostrychnine (17,19,6), a reaction involving oxidation of one of the carbon atoms attached to —N(b)— (the product is a carbinolamine). This base has been shown to be a tertiary alcohol, and therefore the system (LV) must be present in strychnine. (Compare the isomerization of nicotine N-oxide (LVI) to the carbinolamine (LVII) (33).)

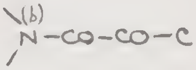
Distillation of strychnine with lime furnishes, in addition to carbazole and indole, β-collidine (LVIII) and tryptamine (LIX) (10). Strychnine must therefore contain a 3,4-substituted pyridine ring, and since —N(a)— is contained in an indole nucleus this must involve —N(b)—, and strychnine must contain the part-structure (LX). The production of tryptamine indicates the points of attach-



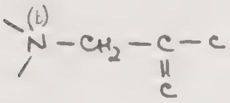
(XLV) (XLVI)



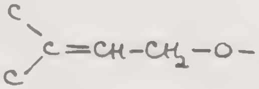
(XLVII)



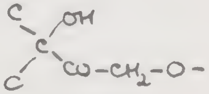
(XLVIII)



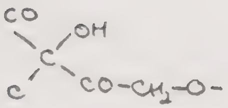
(XLIX)



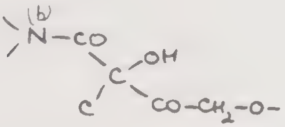
(L)



(LI)



(LII)



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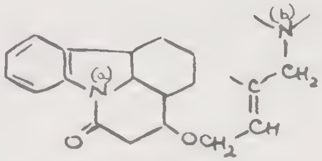

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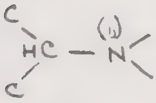
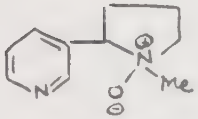


(LV)



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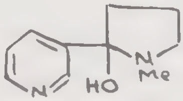

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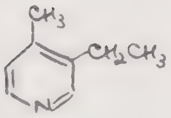

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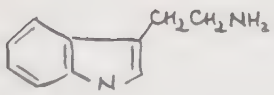

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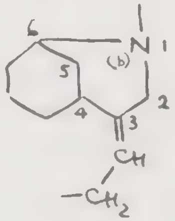
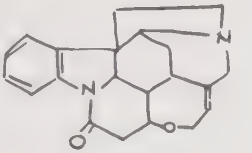


(LX)

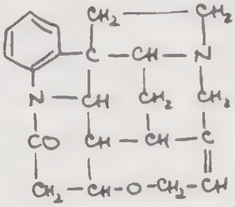
ment of the remaining two unallocated carbon atoms in strychnine, and the alkaloid may be allotted the full structure (LXI), which may also be written as (LXII) (7,15,47).

Full formulas for the other degradation products may now be given as in formulas (LXIII) ⟶ (LXXI). Pseudostrychnine behaves as a carbinolamine and gives *O*-ethers containing the part-structure (LXXIII) and also a normal methiodide (LXXIV) together with the hydriodide of the related ketone (LXXV).

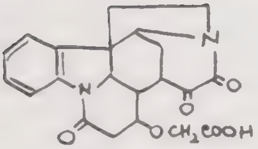
When the quaternary alkylstrychninium salts are heated with methanolic potash the normal Hofmann degradation does not occur, methoxyalkyldihydroneostrychninium salts being obtained instead



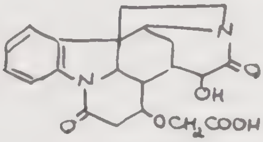
(LXI)



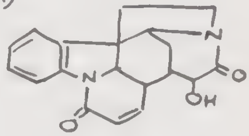
(LXII)



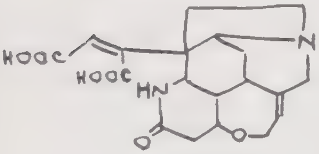
(LXIII)
STRYCHNINONIC ACID



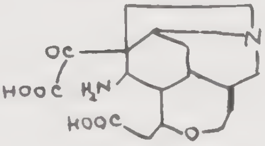
(LXIV)
STRYCHNINOLIC ACID



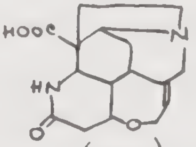
(LXV)
STRYCHNINOLONE-a



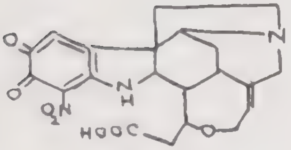
(LXVI)
ACID $C_{19}H_{22}O_6N_2$



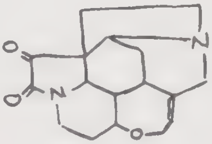
(LXVII)
ACID $C_{17}H_{22}O_6N_2$



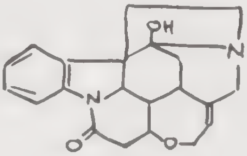
(LXVIII)
ACID $C_{16}H_{20}O_4N_2$



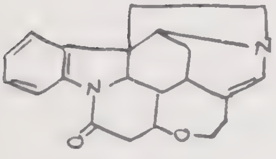
(LXIX)
CACOTHELIN



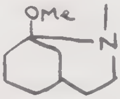
(LXX)
2:3-DIKETONUCIDINE



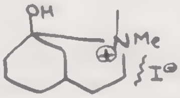
(LXXI)
ψ-STRYCHNINE



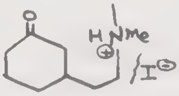
(LXXII)
NEOSTRYCHNINE



(LXXIII)



(LXXIV)

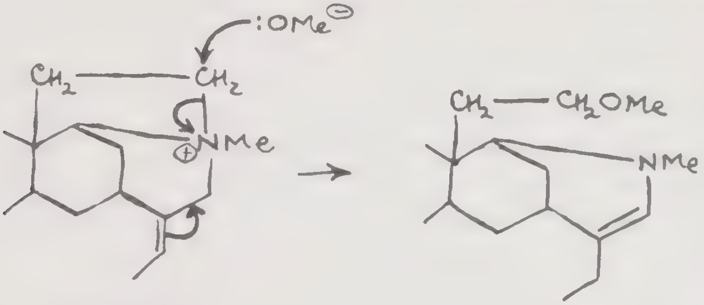


(LXXV)

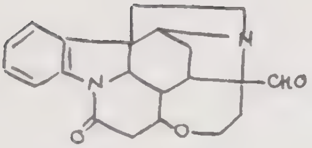
by the process (LXXVI) ⟶ (LXXVII). When these salts are heated with dilute hydrochloric acid, quaternary alkylneostrychninium salts are obtained, and these on heating lose alkyl chloride giving neostrychnine, isomeric with strychnine. This base can also be obtained by heating strychnine with Raney nickel in boiling xylene (8). It is converted into dihydrostrychnine on hydrogenation and so must differ from strychnine only in the position of a double bond. The same process can be carried out with strychnidine giving neostrychnidine. These neo bases are vinylamines, and neostrychnine may be allotted the structure (LXXII), in support of which may be cited the fact that it can be oxidized to an aldehyde (LXXVIII), a process that involves the rearrangement of $-\mathrm{N}-\mathrm{CH}=\mathrm{C}$ to $-\mathrm{N}-\mathrm{C}-\mathrm{CHO}$.

Exhaustive methylation of dihydrostrychnidine-A affords the following substances (1,2,3). In the first step the bases (LXXIX) and (LXXX); in the second step the bases (LXXXI) and (LXXXII) from (LXXIX) and the bases (LXXXII) and (LXXXIII) from (LXXX), and finally the substance (LXXXIV) from the bases (LXXXI) and (LXXXII).

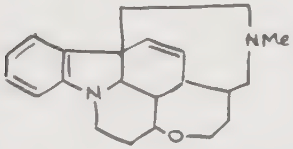
The oxidation of dihydrostrychninolone affords the α-keto-amide dihydrostrychninone (LXXXV), which may be further oxidized with



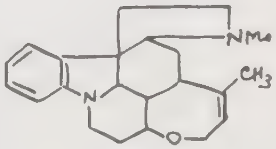
(LXXVI) (LXXVII)



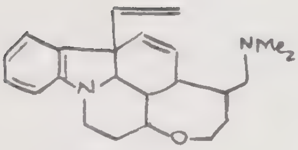
(LXXVIII)



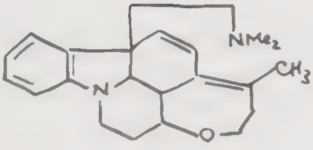
(LXXIX)



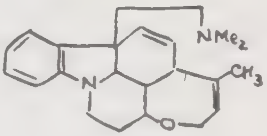
(LXXX)



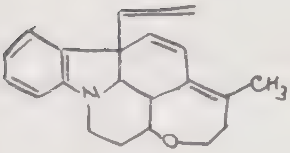
(LXXXI)



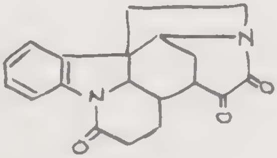
(LXXXII)



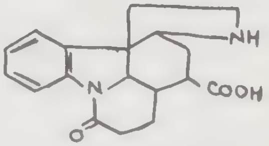
(LXXXIII)



(LXXXIV)



(LXXXV)



(LXXXVa)

hydrogen peroxide to cunine carboxylic acid (LXXXVa); this acid on heating gives a lactam (34).

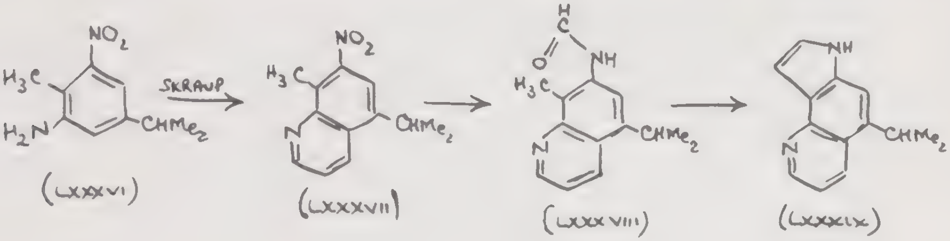
B. Vomicine (CXX).

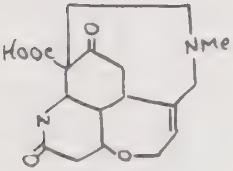
This alkaloid, which has the composition $C_{22}H_{24}O_4N_2$, has been isolated from the residues of the preparation of strychnine. The isolation of the two alkaloids from the same source suggests a structural similarity between them, and this is borne out by the reactions of vomicine. The alkaloid can be converted into vomicinic acid, vomicidine, and desoxyvomicine, analogous to strychnic acid, strychnidine, and desoxystrychnine. Vomicine, like strychnine, contains one basic and one nonbasic nitrogen atom; it contains one phenolic hydroxyl group and one ketonic carbonyl group (44).

Vomicine can be dehydrated by heating with palladium at 250° to vomipyrine, $C_{15}H_{16}N_2$ (43), which has been shown to have the structure (XC) by the synthesis shown, (LXXXVI) ⟶ (XC) (36).

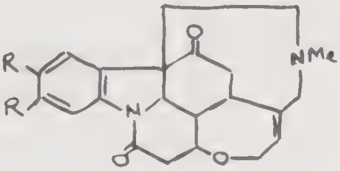
Oxidation of vomicine with chromic acid affords three acids (42, 44,45,46), $C_{16}H_{20}O_3N_2 \cdot 3H_2O$, $C_{17}H_{22}O_5N_2 \cdot 3H_2O$ (this is the chief product), and $C_{16}H_{20}O_6N_2 \cdot 5H_2O$. Of these the most important is the acid $C_{17}H_{22}O_5N_2 \cdot 3H_2O$ as it may also be prepared by the oxidation of *N*-methyl-*sec*-pseudostrychnine (XCI, R = H) and *N*-methyl-*sec*-pseudobrucine (XCI, R = OMe). The acid may therefore be allotted the structure (XCII) and vomicine must be a hydroxy-*N*-methyl-*sec*-pseudostrychnine, probably of structure (XCIII) (5).

The acid (XCII) can be decarboxylated to the amide (XCIV) and catalytically reduced to the dihydro compound (XCV). During the reduction another product is formed by decarboxylation and reduction of the amide group; this has the composition $C_{16}H_{26}O_2N_2$, is relatively stable toward permanganate, is strongly alkaline, and yields a monobenzoyl derivative; it presumably has the structure (XCVI).

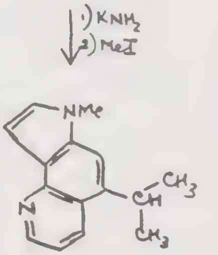




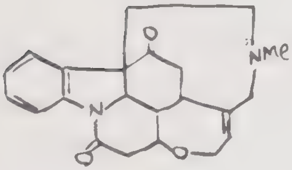
(xcii)



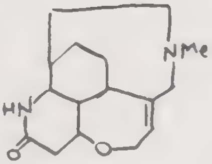
(xci)



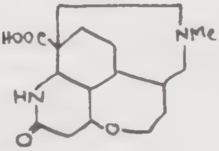
(xc)



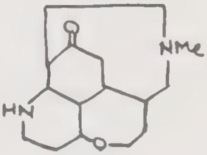
(xciii)



(xciv)



(xcv)



(xcvi)

C. The Total Synthesis of Strychnine.

The total synthesis of strychnine has recently been achieved by Woodward and his co-workers by the route shown in formulas (XCVII) ⟶ (CXXIII) (48). The term "relay" is used to denote a compound prepared by synthesis and identified with material prepared by degradation, the degradation product then being used for further stages in the synthesis.

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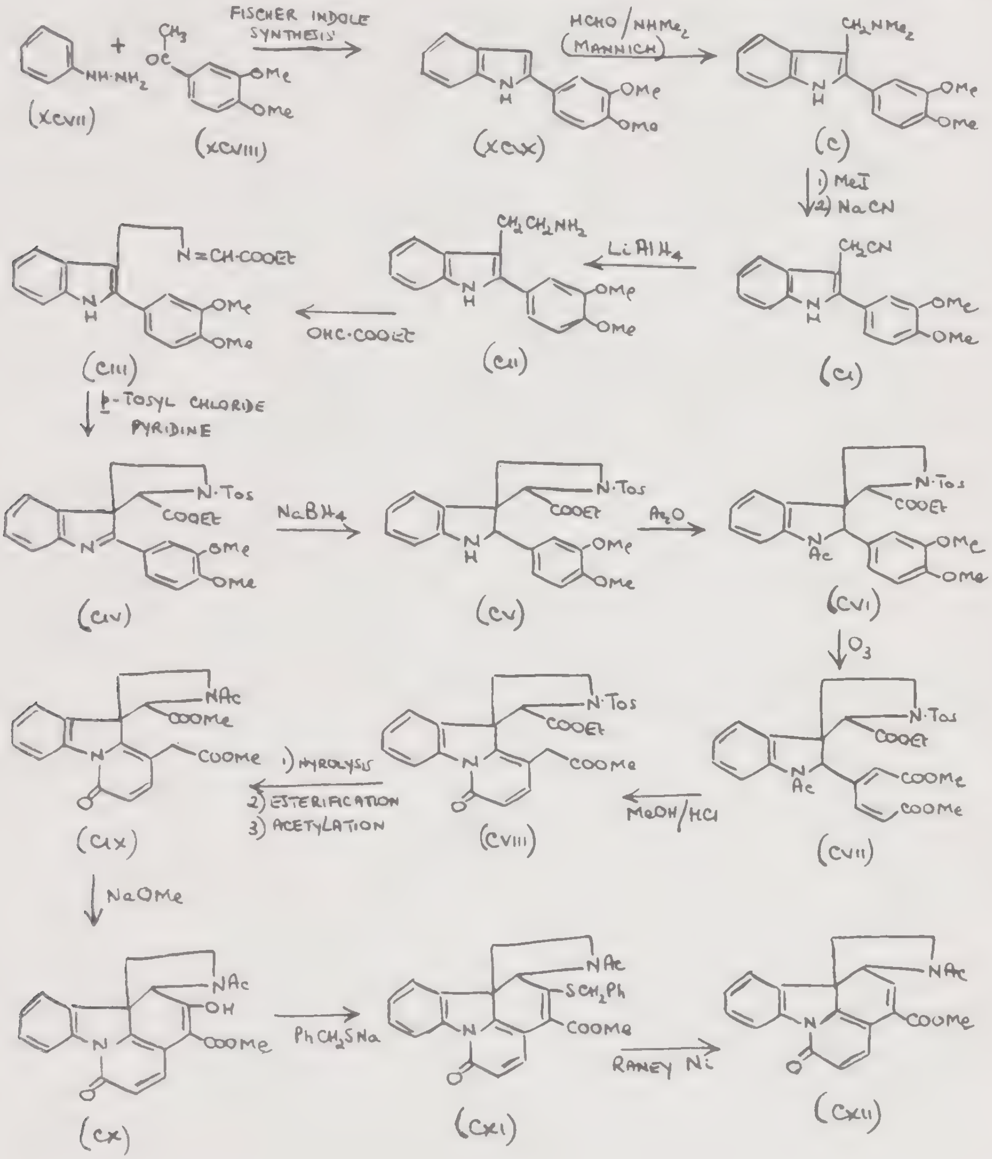
(XCVII)
(XCVIII)
FISCHER INDOLE SYNTHESIS
(XCIX)
HCHO/NHMe₂ (MANNICH)
(C)
1) MeI 2) NaCN
(CI)
LiAlH₄
(CII)
OHC·COOEt
(CIII)
p-TOSYL CHLORIDE PYRIDINE
(CIV)
NaBH₄
(CV)
Ac₂O
(CVI)
O₃
(CVII)
MeOH/HCl
(CVIII)
1) HYDROLYSIS 2) ESTERIFICATION 3) ACETYLATION
(CIX)
NaOMe
(CX)
PhCH₂SNa
(CXI)
RANEY Ni
(CXII)

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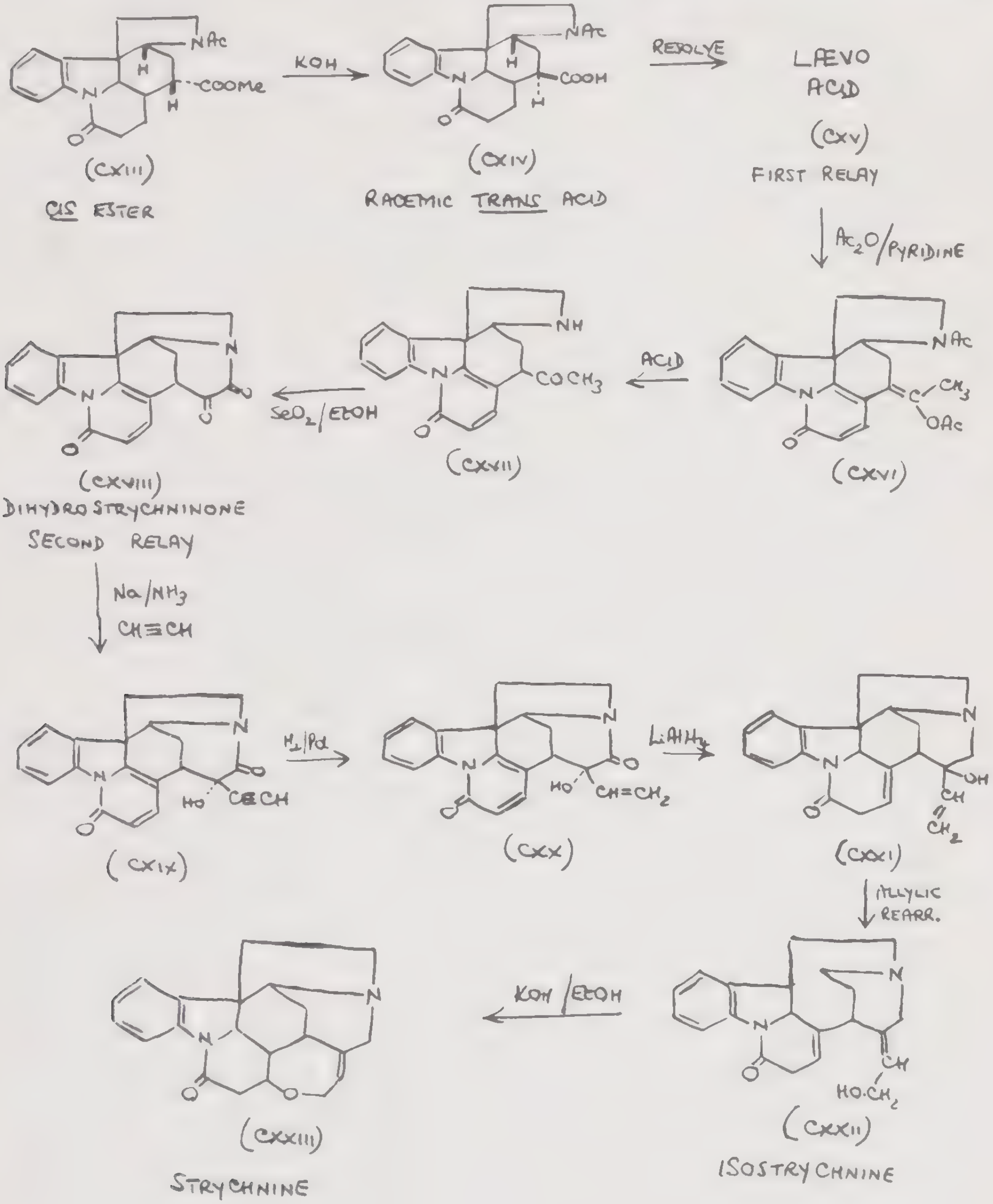

NAc
COOMe
H
N
O
(CXIII)
CIS ESTER
KOH
COOH
(CXIV)
RACEMIC TRANS ACID
RESOLVE
LAEVO ACID
(CXV)
FIRST RELAY
Ac₂O/PYRIDINE
CH₃
OAc
(CXVI)
ACID
NH
COCH₃
(CXVII)
SeO₂/EtOH
(CXVIII)
DIHYDROSTRYCHNINONE
SECOND RELAY
Na/NH₃
CH≡CH
HO
C≡CH
(CXIX)
H₂/Pd
CH=CH₂
(CXX)
LiAlH₄
OH
CH
CH₂
(CXXI)
ALLYLIC REARR.
CH
HO·CH₂
(CXXII)
ISOSTRYCHNINE
KOH/EtOH
(CXXIII)
STRYCHNINE

THE ERYTHRINA ALKALOIDS

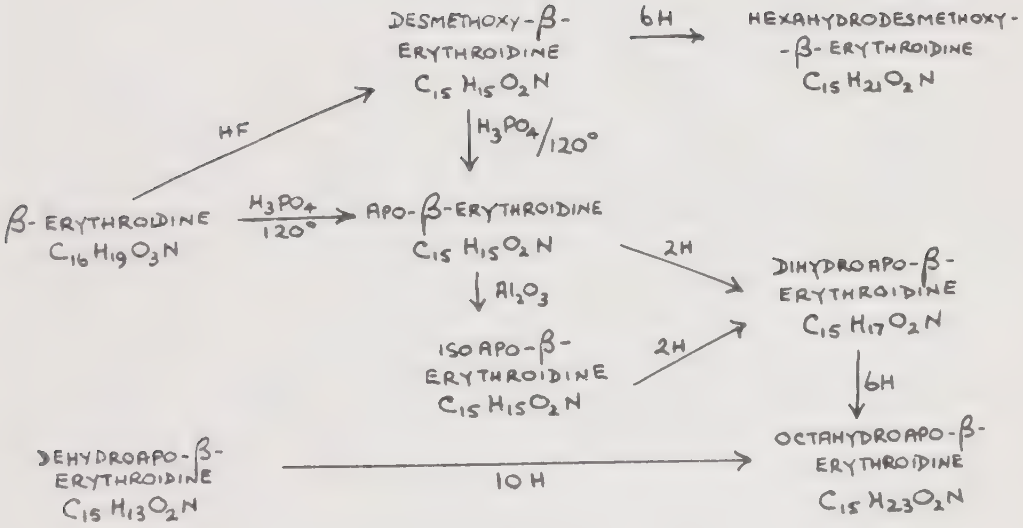
A considerable number of alkaloids have been isolated from *Erythrina* species, and the elucidation of their constitution has been achieved mainly by Prelog, who first suggested the nature of the ring system present in the bases, and by Boekelheide.

1. THE ERYTHROIDINE GROUP

A. **β-Erythroidine (XXXIII).**

This base was first isolated by Folkers (7) from the seeds of *Erythrina americana* Mill. It has the composition $C_{16}H_{19}O_3N$ and contains two reducible double bonds (6). Three stages of exhaustive methylation are necessary for complete removal of the nitrogen atom, which must therefore be common to two rings. It contains a lactone ring and dissolves in warm aqueous potassium hydroxide as the salt of a hydroxy-acid (8). On fusion with potassium hydroxide the alkaloid gives indole (9).

On treatment with anhydrous hydrofluoric acid β-erythroidine loses the elements of methanol, giving desmethoxy-β-erythroidine which may be hydrogenated to a hexahydro derivative. Molecular rearrangement accompanies loss of methanol when β-erythroidine is heated with phosphoric acid at 120°, the product being apo-β-erythroidine, isomeric with desmethoxy-β-erythroidine, from which it may be prepared by heating with phosphoric acid. Apo-β-erythroidine is converted into isoapo-β-erythroidine over aluminum oxide; this change involves the migration of a double bond, and both compounds give the same dihydro derivative (14).

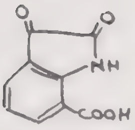

DESMETHOXY-β-ERYTHROIDINE
$C_{15}H_{15}O_2N$
6H
HEXAHYDRODESMETHOXY-β-ERYTHROIDINE
$C_{15}H_{21}O_2N$
HF
H_3PO_4/120°
β-ERYTHROIDINE
$C_{16}H_{19}O_3N$
H_3PO_4
120°
APO-β-ERYTHROIDINE
$C_{15}H_{15}O_2N$
2H
DIHYDROAPO-β-ERYTHROIDINE
$C_{15}H_{17}O_2N$
Al_2O_3
ISOAPO-β-ERYTHROIDINE
$C_{15}H_{15}O_2N$
2H
6H
DEHYDROAPO-β-ERYTHROIDINE
$C_{15}H_{13}O_2N$
10 H
OCTAHYDROAPO-β-ERYTHROIDINE
$C_{15}H_{23}O_2N$

Apo-β-erythroidine when heated with platinum oxide suffers dehydrogenation to dehydroapo-β-erythroidine; during this process no catalyzed rearrangement takes place for the product may be hydrogenated to octahydroapo-β-erythroidine, also obtainable by the further reduction of dihydroapo-β-erythroidine (11). Dehydroapo-β-erythroidine may be oxidized by alkaline permanganate to 7-carboxyisatin (I), 2-aminoisophthalic acid (II), and 3,8-dicarboxy-4-hydroxyquinoline (III). The acids (I) and (II) may be obtained in the same way from β-erythroidine (11).

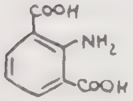
The infrared spectrum of apo-β-erythroidine suggests that the lactone ring is six-membered and that this base is a derivative of dihydroindole and contains the part-structure (IV); such a compound would be expected to suffer easy dehydrogenation to the corresponding indole, and this process corresponds to the conversion of apo-β-erythroidine into the dehydroapo base.

Apo-β-erythroidine contains two $—CH_2—CH_2—$ groupings attached to the nitrogen atom, as was demonstrated by the results of Hofmann degradation. The product of the first stage of exhaustive methylation of the apo base, des-*N*-methylapo-β-erythroidine (VI) was shown to contain the group $—CH{=}CH_2$ by the presence of bands characteristic of this group in the infrared spectrum, and by the production of formaldehyde on ozonolysis of the base. Hydrogenation of the base (VI) afforded the dihydro derivative (VII), which on further degradation afforded dihydrodes-*N*;*N*-dimethylapo-β-erythroidine (VIII) and this was, as before, shown to contain the group $—CH{=}CH_2$. Accordingly, assuming the size of the lactone ring (see below), apo-β-erythroidine may be alloted the structure (V).

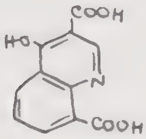
The fact that the seven-membered ring of (V) is opened during the first stage of degradation was proved as follows. The change apo- → isoapo-β-erythroidine involves the migration of the double bond in the lactone ring into conjugation with the carbonyl group; similarly, over alumina, the base (VI) may be isomerized to (IX) which gives acetaldehyde on ozonolysis, as is required by the structure (IX). This base (IX) on reduction with lithium aluminum hydride affords the diol (X), which may be reduced to the dihydro derivative (XI), identical with the compound prepared from the dihydro-methine


O
O
NH
COOH

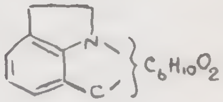
(i)


COOH
NH$_2$
COOH

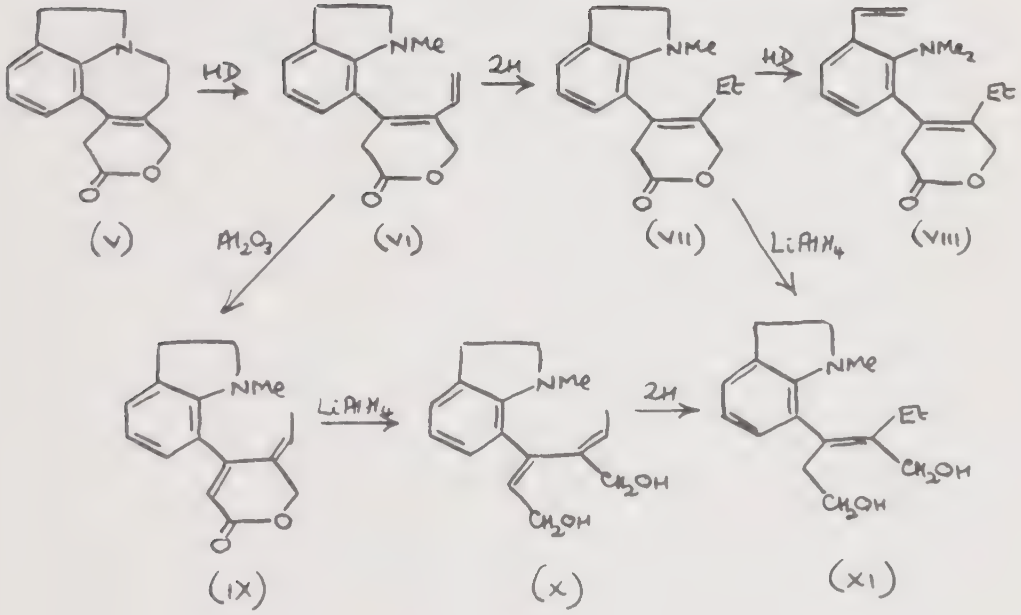
(ii)


COOH
HO
N
COOH

(iii)


N
C
C$_6$H$_{10}$O$_2$

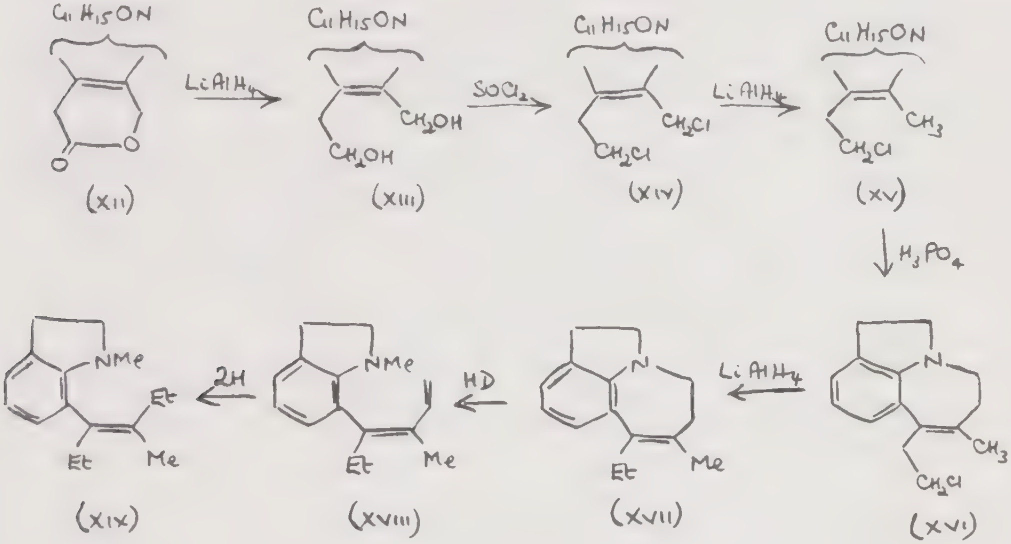
(iv)


N
(v)
HD
NMe
(vi)
2H
NMe
Et
(vii)
HD
NMe$_2$
Et
(viii)
Al$_2$O$_3$
LiAlH$_4$
NMe
(ix)
LiAlH$_4$
NMe
CH$_2$OH
CH$_2$OH
(x)
2H
NMe
Et
CH$_2$OH
CH$_2$OH
(xi)

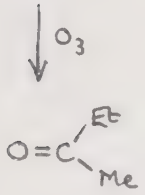
base (VII), showing that no skeletal rearrangement is involved in the apo- ⟶ isoapo- transformation (12).

The size of the lactone ring in apo-β-erythroidine was confirmed in the following way. Lithium aluminum hydride reduction of β-erythroidine (XII) gives β-erythroidinol (XIII), which can be converted into the dichloro compound (XIV), and this yields the monochloro base (XV) on reduction with lithium aluminum hydride. Subjection of the base (XV) to the apo rearrangement leads to the base (XVI), which may be further reduced to desoxyapo-β-erythroidinol (XVII), which is not directly accessible from apo-β-erythroidinol (XX) owing to the ready formation of the cyclic ether (XXI). Hofmann degradation of the desoxy compound (XVII) affords the methine (XVIII), reduction of which furnishes the dihydromethine (XIX). Ozonolysis of the dihydromethine (XIX) gives methyl ethyl ketone. These results, together with the fact that β-erythroidine derivatives contain no $-\mathrm{C}-\mathrm{CH}_3$ groups (thus ruling out five-membered ring structures) effectively demonstrate the size of the lactone ring and the positions of the oxygen atom and the double bond (13).

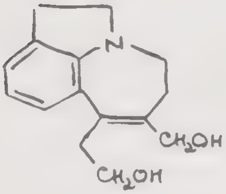
The Hofmann degradation of dihydro-β-erythroidine affords a normal methine base $C_{17}H_{23}O_3N$, and an abnormal base $C_{15}H_{19}N$, which is an *o*-substituted styrene that gives phthalic acid on oxidation.



$C_{11}H_{15}ON$
(XII)
LiAlH$_4$
$C_{11}H_{15}ON$
CH$_2$OH
CH$_2$OH
(XIII)
SOCl$_2$
$C_{11}H_{15}ON$
CH$_2$Cl
CH$_2$Cl
(XIV)
LiAlH$_4$
$C_{11}H_{15}ON$
CH$_3$
CH$_2$Cl
(XV)
H$_3$PO$_4$
N
CH$_3$
CH$_2$Cl
(XVI)
LiAlH$_4$
N
Et
Me
(XVII)
HD
NMe
Et
Me
(XVIII)
2H
NMe
Et
Et
Me
(XIX)

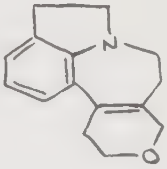


O$_3$
O=C
Et
Me



N
CH$_2$OH
CH$_2$OH

(XX)



N
O

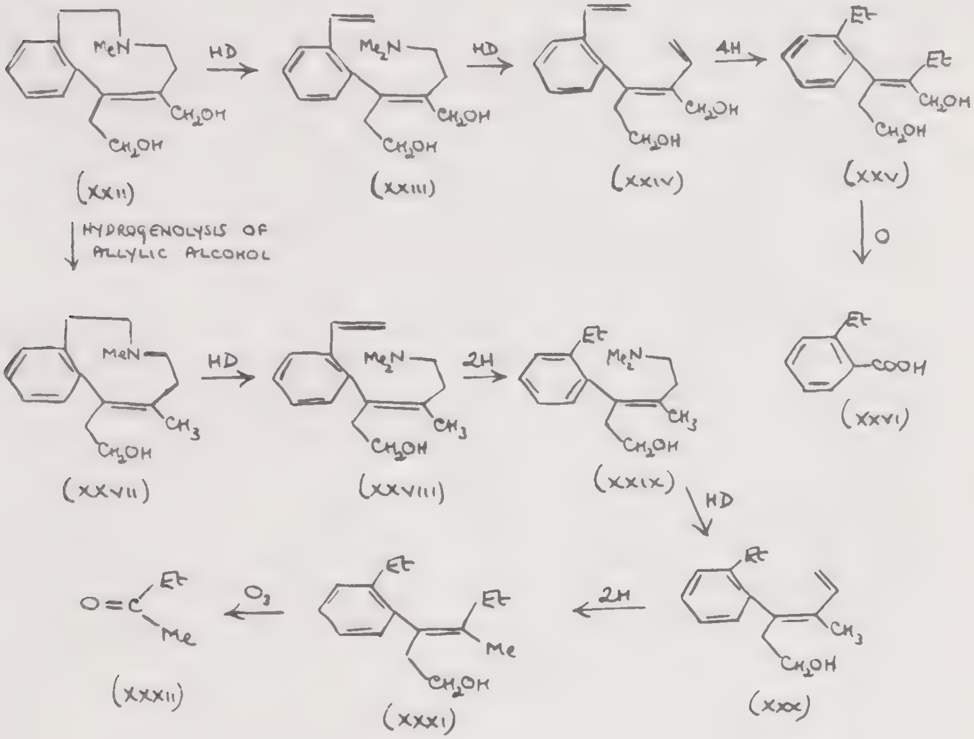
(XXI)

Methyl alcohol is lost and a single base $C_{16}H_{23}O_2N$ is formed during the degradation of dihydro-β-erythroidinol, the product of lithium aluminum hydride reduction of dihydro-β-erythroidine (1). This base was shown by spectral studies to be an *o*-substituted styrene, having a fully substituted double bond. When subjected to a second Hofmann degradation it yields an oily base that may be further degraded to desazadihydro-β-erythroidinol. This nitrogen-free product may be reduced, at the double bonds introduced during the last two stages of exhaustive methylation, to a tetrahydro compound, the fully substituted styrene double bond being unaffected, the tetrahydro compound gives *o*-ethylbenzoic acid (XXVI) on oxidation.

The structure (XXII) for des-*N*-methyldihydro-β-erythroidinol explains these reactions quite satisfactorily, as shown in the formulas (XXII) → (XXVI) (16).

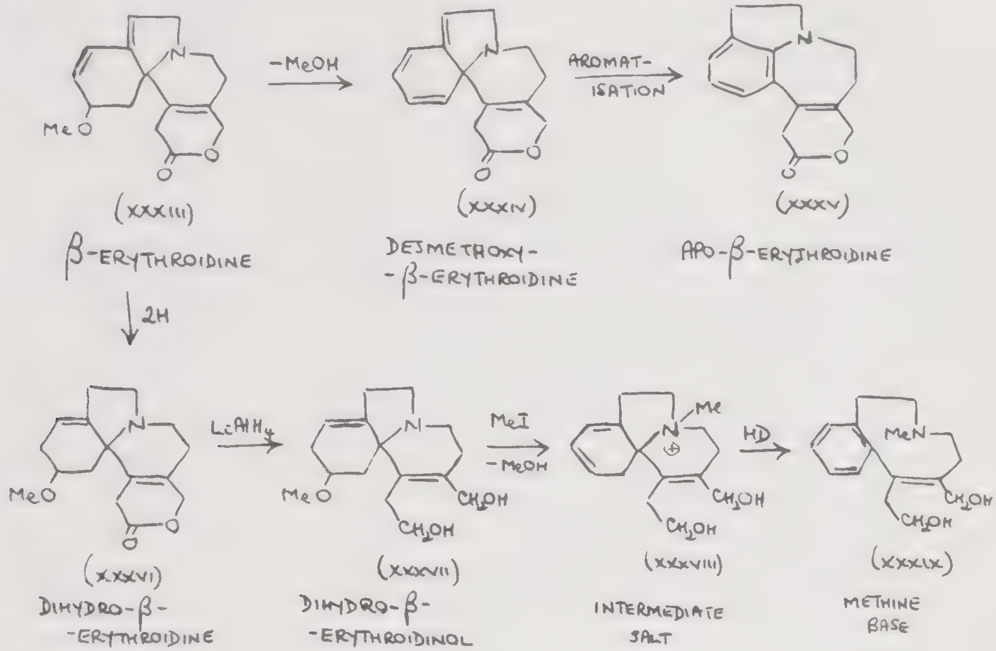
These conclusions are supported by the degradation of des-*N*-methyldesoxydihydro-β-erythroidinol (XXVII), prepared by the hydrogenolysis of the allylic alcohol system of (XXII). This compound gives a methine base (XXVIII) which may be reduced to the dihydromethine (XXIX) and then further degraded to the nitrogen-free substance (XXX). Both the methine (XXVIII) and the nitrogen-free product (XXX) were shown to contain the system $-CH=CH_2$, therefore the nitrogen atom in (XXVII) and hence in (XXII) must be flanked by two $-CH_2-CH_2-$ systems.

The nitrogen-free product (XXX) may be reduced to the dihydro compound (XXXI) which affords methyl ethyl ketone on ozonolysis. This result shows that the $-CH_2OH$ and $-CH_2-CH_2OH$ groups in (XXII) must be in the positions shown and not reversed, and, since (XXII) is obtained by the lithium aluminum hydride reduction of dihydro-β-erythroidine, it is an indirect proof of the nature of the lactone ring in this substance (16).


MeN
CH₂OH
CH₂OH
(XXII)
HD
Me₂N
CH₂OH
CH₂OH
(XXIII)
HD
CH₂OH
CH₂OH
(XXIV)
4H
Et
Et
CH₂OH
CH₂OH
(XXV)
HYDROGENOLYSIS OF ALLYLIC ALCOHOL
O
MeN
CH₃
CH₂OH
(XXVII)
HD
Me₂N
CH₃
CH₂OH
(XXVIII)
2H
Et
Me₂N
CH₃
CH₂OH
(XXIX)
Et
COOH
(XXVI)
HD
Et
CH₃
CH₂OH
(XXX)
2H
Et
Et
Me
CH₂OH
(XXXI)
O₃
O=C
Et
Me
(XXXII)

Of the possible formulas the only logical arrangement that accounts satisfactorily for the production of apo-β-erythroidine and des-*N*-methyldihydro-β-erythroidinol is a spiro structure such as (XXXIII) (3). The elimination of the elements of methanol from (XXXIII) would give desmethoxy-β-erythroidine (XXXIV), which could then undergo carbonium ion rearrangement to apo-β-erythroidine (XXXV) (compare the transformation of (XL) to (XLI) (15) and of santonin (XLII) to desmotroposantonin (XLIII) (5), and also the suggested mechanism for the transformation of thebaine into morphothebaine (Chapter 5)).

β-Erythroidine contains two reducible double bonds and one (the full-substituted double bond of the lactone ring) that resists hydrogenation. A careful study of the ultraviolet spectrum of the alkaloid has led to the placing of these reducible double bonds in the positions shown in the structure (XXXIII) (3). The position of the methoxyl group is indicated by the results of the degradation of β-erythroidinol (XLV). Hofmann degradation of this base involves aromatization without loss of the methoxyl group, the product being des-*N*-methyl-β-erythroidinol (XLV), which has the infrared spectrum of a typical 1,2,3-trisubstituted benzene and gives 4-methoxyphthalic acid on oxidation, i.e., (XLV) → (XLVI) (3).



(XXXIII) β-ERYTHROIDINE

(XXXIV) DESMETHOXY-β-ERYTHROIDINE

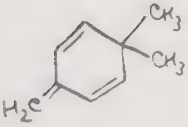
(XXXV) APO-β-ERYTHROIDINE

(XXXVI) DIHYDRO-β-ERYTHROIDINE

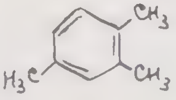
(XXXVII) DIHYDRO-β-ERYTHROIDINOL

(XXXVIII) INTERMEDIATE SALT

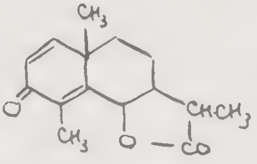
(XXXIX) METHINE BASE



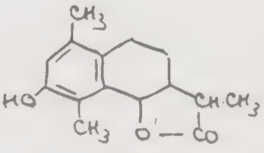
(XL)



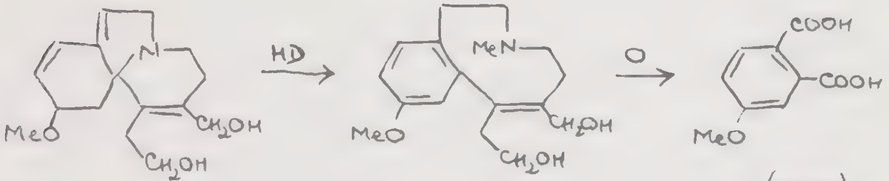
(XLI)



(XLII)



(XLIII)



(XLIV)

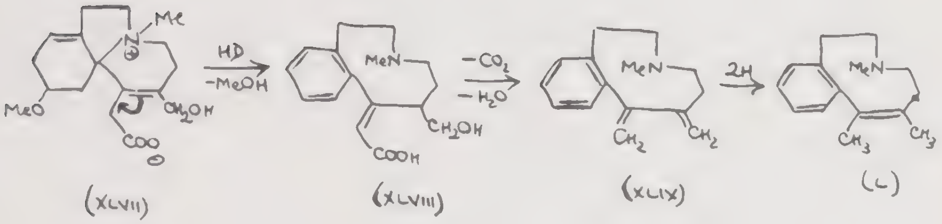
(XLV)

(XLVI)

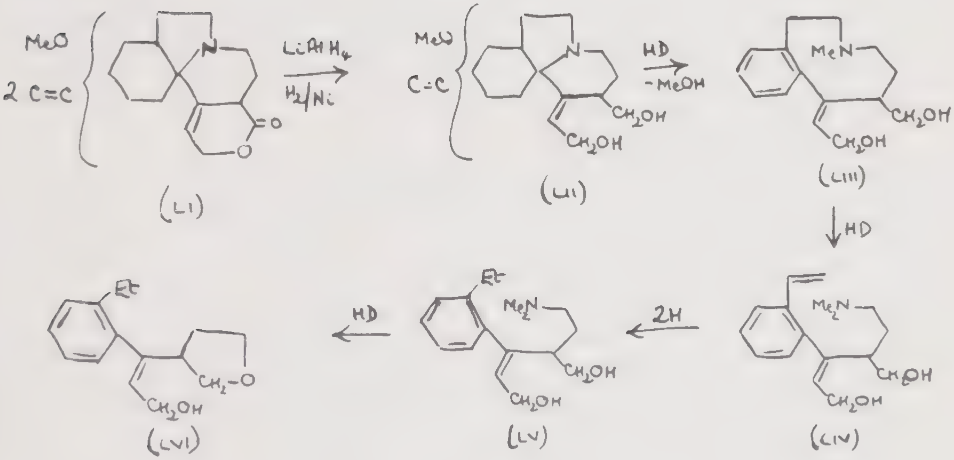
The base $C_{15}H_{19}N$ obtained during the Hofmann degradation of dihydro-β-erythroidine (1) has the typical ultraviolet spectrum of a styrene, and the infrared spectrum shown the presence in the molecule of a $>C=CH_2$ group. This group disappears during hydrogenation to a dihydro compound, but the styrene chromophore remains. These results could be explained by the structures (XLIX) and (L) for the base and its dihydro derivative. Hofmann degradation of the quaternary salt of dihydro-β-erythroidine (formulated as the betaine (XLVII)) with scission of the spiro-nitrogen linkage would give (XLVIII), with loss of methanol and aromatization. This product, being a cinnamic acid derivative, would be expected to suffer decarboxylation and dehydration giving (XLIX); 1,4-reduction of the diene system of (XLIX) would then afford the dihydro derivative (L), the fully substituted double bond of which would resist hydrogenation (3). Normal Hofmann degradation of the salt (XLVII) would yield one of the two possible vinyl compounds.

B. α-Erythroidine (LI).

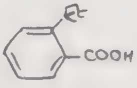
This base, which occurs with β-erythroidine, is isomeric with the latter. It was first thought to be a diastereoisomer of β-erythroidine, but this was quickly disproved when it was found that desmethoxy-α-erythroidine is neither identical with nor the optical antipode of desmethoxy-β-erythroidine (2). It has been shown to have the structure (LI), by the degradation of dihydro-α-erythroidinol (LII) through the bases (LIII), (LIV), and (LV) to the nitrogen-free product (LVI), which on oxidation afforded o-ethylbenzoic acid (LVII) and the ketone (LVIII) (2,10). α-Erythroidine thus differs from the β-isomer in the arrangement of the lactone ring. The position of the methoxyl group and the two double bonds in (LI) has not yet been determined; they may well occupy the same positions as in the β-isomer, with both alkaloids being derived from the same precursor (see Chapter 11).



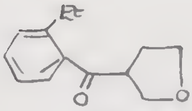
(XLVII) (XLVIII) (XLIX) (L)



(LI) (LII) (LIII) (LIV) (LV) (LVI)



(LVII)



(LVIII)

2. THE ERYSOPINE GROUP

A. Erysopine (LIX), Erysovine, Erysodine, and Erythraline.

The spiro type of structure postulated for β-erythroidine was first suggested for the erythrina alkaloids by Prelog and his coworkers during an investigation of four simpler alkaloids. The parent compound of this group is erysopine (LIX); erysovine and erysodine are the two isomeric monomethyl ethers and erythraline is the methylene ether of erysopine.

When erysodine is heated with hydrochloric acid it is converted into desmethylerysodine (LX), which on further treatment with acids gives apoerysodine (LXI). Apoerysodine may be hydrogenated to hexahydroapoerysodine (LXII) and may also be made to undergo carbonium ion rearrangement of the β-erythroidine → apo-β-erythroidine type to apoerysopine (LXIII), also obtainable from erythraline and erysopine (4).

Apoerysopine may be converted into the dimethyl ether methine (LXIV) and finally, after further Hofmann degradation and reduction, into the diphenyl derivative (LXV).

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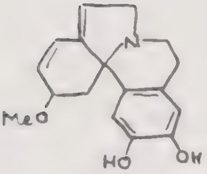
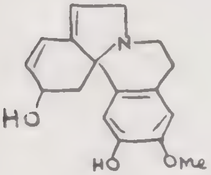
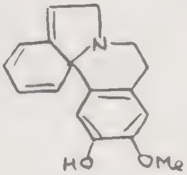


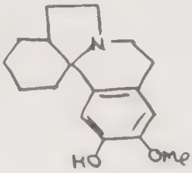
(LIX)



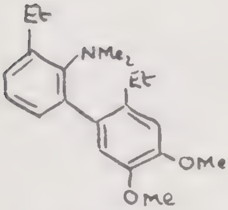
(LX)



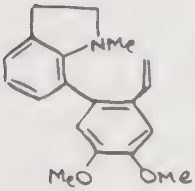
(LXI)



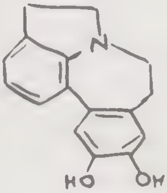
(LXII)



(LXV)



(LXIV)



(LXIII)

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CHAPTER 10

COLCHICINE (XXXIII) or (XXXIV)

The alkaloid colchicine occurs in the meadow saffron, *Colchicum autumnale* L. It possesses the remarkable specific property of being able to halt cell division at a particular stage, and this has led directly to the artificial production of polyploid varieties of many plants.

Colchicine, $C_{22}H_{25}O_6N$, contains five groupings that can suffer hydrolysis under varying conditions. It may be hydrolyzed by acids to methanol and colchiceine, $C_{21}H_{23}O_6N$; this process was first regarded as the hydrolysis of a carboxylic ester, but is now known to be the hydrolysis of an enol methyl ether. Further hydrolysis with hydrochloric acid results in the loss of acetic acid and the appearance of a primary amino group, the product being trimethylcolchicinic acid, $C_{19}H_{21}O_5N$, from which it is concluded that colchicine contains the grouping —NHAc (28).

Trimethylcolchicinic acid contains three —OMe groups which may be successively hydrolyzed to —OH by acids. The fifth oxygen atom not accounted for by the four groups so far specified has been indirectly established as being present in an unreactive carbonyl group.

Since the hydrolysis of colchicine to colchiceine involves the change —OMe → —OH + MeOH, it should be possible to reverse the process providing no other transformation occurs simultaneously, and this has been achieved by the treatment of the sodium salt of colchiceine with methyl iodide, when colchicine and *N*-methylcolchicine are obtained (16). Colchicine and an isomer of this alkaloid, isocolchicine, are obtained when colchiceine is methylated

with diazomethane (17,20). This isomerism of colchicine and isocolchicine has considerable structural implications; a similar isomerism exists in the two *O*:*N*-dibenzenesulfonyl derivatives of trimethylcolchicinic acid, both of which may be hydrolyzed to the same *N*-benzenesulfonyl derivative (24). Grewe (15) has claimed the production of a new isomer of colchicine, lumicolchicine, by the irradiation of colchicine in aqueous solution with ultraviolet light.

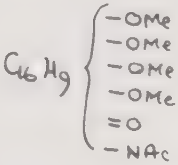
Colchicine may thus be written as (I), and the parent hydrocarbon would be $C_{16}H_{16}$, which is eighteen hydrogen atoms less than the corresponding paraffin $C_{16}H_{34}$. Catalytic hydrogenation of colchicine affords hexahydrocolchicine, in which two double bonds and the carbonyl group have been reduced; this base contains one double bond, so colchicine itself must contain three double bonds (6). In addition the alkaloid contains an aromatic nucleus (trimethyl colchicinic acid is the trimethyl ether of a trihydric phenol and may be oxidized to 3,4,5-trimethoxyphthalic acid) (23). The fully reduced hydrocarbon corresponding to colchicine would therefore have the composition $C_{16}H_{28}$ ($C_{16}H_{16}$ + 6H for three double bonds + 6H for the aromatic nucleus), compared with $C_{16}H_{34}$ for the C_{16}-paraffin, and hence colchicine must contain three rings (9).

The Phenanthrene Structure. It was suggested by Windaus that colchicine has a hydrogenated phenanthrene skeleton and that the structure of the alkaloid was in fact (II), on the following grounds.

(*a*) Colchicine can be converted into colchiceine (III) which, on heating with alkaline potassium iodide affords iodo-*N*-acetylcolchinol (IV); this, it was claimed, was a characteristic reaction of hydroxymethylene ketones in the isomeric hydroxyaldehyde form (XI) (26).

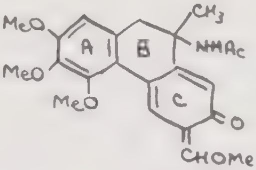
(*b*) The methyl ether of iodo-*N*-acetylcolchinol may be reduced to *N*-acetylcolchinol methyl ether, (V, R = Ac), hydrolysis of which affords colchinol methyl ether (V, R = H). This base may be oxidized to 4-methoxyphthalimide, showing that it contains the system (VIII) (26).

(*c*) Exhaustive methylation of colchinol methyl ether leads to the tetramethoxy compound deaminocolchinol methyl ether, distillation of which with zinc dust affords 9-methylphenanthrene (VII), identical with an authentic specimen (25,27). Deaminocolchinol methyl ether was accordingly allotted the constitution (VI).

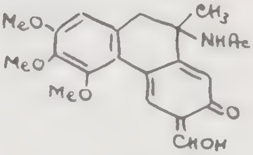


$C_{16}H_9\left\{\begin{array}{l}-OMe\\-OMe\\-OMe\\-OMe\\=O\\-NAc\end{array}\right.$

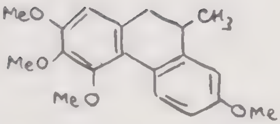
(I)



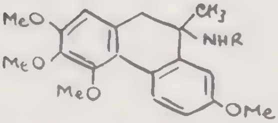
(II)



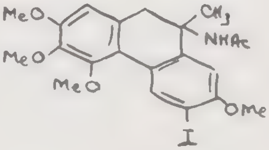
(III)



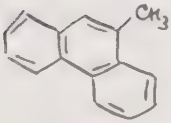
(VI)



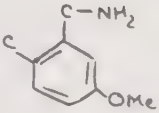
(V)



(IV)



(VII)



(VIII)

(*d*) Colchicine and colchinol may be oxidized to 3,4,5-trimethoxyphthalic acid (23). An acid, allotted the constitution (IX), may be obtained by the oxidation of *N*-benzoyltrimethylcolchicinic acid, and on demethylation this acid is converted into a lactone, formulated as (X), showing that the methoxyl groups in the aromatic ring-A must be orientated with respect to ring-B as shown in structure (II) and not as in (XII) (24,26).

(*e*) Fusion of colchicine with potassium hydroxide followed by oxidation results in the production of terephthalic acid and benzene-1,2,4-tricarboxylic acid, and these were believed to be derived from ring-B, which was consequently regarded as being six-membered (25).

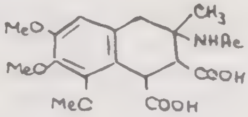
(*f*) The methyl group was placed as shown in (I) to leave a reactive methylene group adjacent to the aromatic ring in order to explain the oxidation of colchicine to a ketone, oxycolchicine, which was formulated as (XIII).

The structure (II), however, has several unsatisfactory features. In particular colchicine shows no tendency to isomerize to the *o*-hydroxyaldehyde form (XI), and the evidence for the size of ring-B is based on the results of oxidation following fusion with potassium hydroxide at 245°.

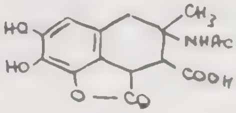
Modification of the formula took place in two stages.

Ring-B. The first indication that the structure (II) for colchicine was incorrect was obtained from a study of the nitrogen-free substance deaminocolchinol methyl ether. This compound, more simply obtained by the elimination of acetamide from *N*-acetylcolchinol methyl ether by heating the amide with phosphorus pentoxide (11), was formulated by Windaus as 2,3,4,7-tetramethoxyphenanthrene (VI), but is not identical with material of this structure prepared by synthesis, nor is it identical with the 2,3,4,6-tetramethoxy compound, which could arise from the structure (II) if the $C{=}CH(OH)$ and $C{=}O$ groups were transposed (4).

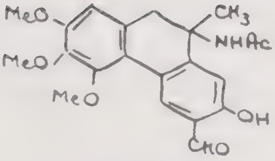
Colchinol methyl ether would be expected to lose ammonia very easily on the basis of the structure (V, R = H) with the production of a fully aromatic phenanthrene; this reaction is not observed. The alternative structure with the $-NH_2$ group in the side chain (XIV) may also be rejected since dehydrogenation of colchinol derivatives to fully aromatic bases cannot be accomplished.



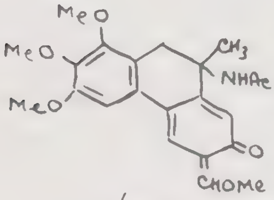
(ix)



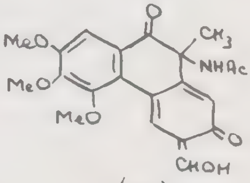
(x)



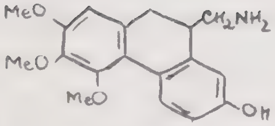
(xi)



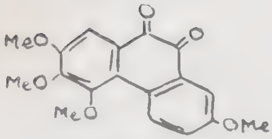
(xii)



(xiii)



(xiv)

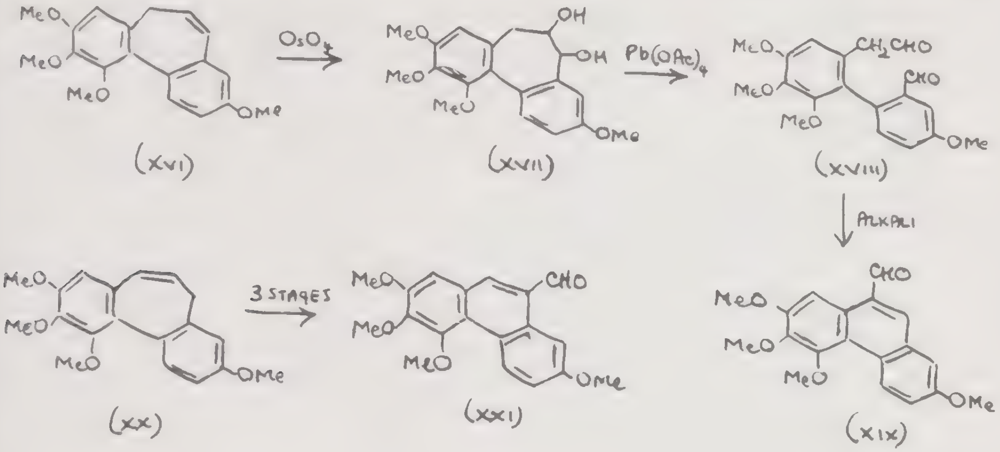


(xv)

Oxidation of deaminocolchinol methyl ether with dichromate affords 2,3,4,7-tetramethoxyphenanthrenequinone (XV), identical with material prepared by synthesis (3), thus confirming the position of the four methoxyl groups in the degradation product. Deaminocolchinol methyl ether and an isomer, isodeaminocolchinol methyl ether, are produced by the dehydration of the carbinol obtained by the treatment of colchinol methyl ether with nitrous acid. Both these nitrogen-free substances give the same dihydro compound on hydrogenation and so must differ only in the position of a double bond (3). The two olefins may be oxidized with osmium tetroxide to two isomeric diols, which on further oxidation with lead tetraacetate yield resinous dialdehydes, and these in the presence of traces of alkali are converted into crystalline monoaldehydes. By this process deaminocolchinol methyl ether (XVI) finally yields 2,3,4,7-tetramethoxy-10-phenanthraldehyde (XIX), and isodeaminocolchinol methyl ether (XX) gives 2,3,4,7-tetramethoxy-9-phenanthraldehyde (XXI) (3). These results clearly show that ring-B of colchicine is seven-membered and not, as believed by Windaus, six-membered. Further support for this view is provided by the oxidation of deaminoiodocolchinol methyl ether to the acid (XXII, R = I); this acid may be reduced to the acid (XXII, R = H) (21).

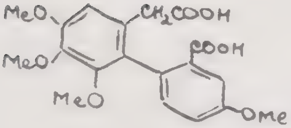
The production of 9-methylphenanthrene from deaminocolchinol methyl ether by demethylation and distillation with zinc dust is paralleled by the production of the same compound by the distillation of 3,4,5,6-dibenzcycloheptatriene (XXIII) with zinc dust (10), and the formation of 2,3,4,7-tetramethoxyphenanthrenequinone (XV) by the oxidation of deaminocolchinol methyl ether is analogous to the formation of phenanthrenequinone by the oxidation of the hydrocarbon (XXIII) (10) and the aldehyde (XXIV) (22).

The seven-membered nature of ring-B in colchicine was finally proved by the synthesis of derivatives, including *N*-acetylcolchinol methyl ether. The unsaturated ketone (XXVIII), formed as a by-product during the oxidation of deaminocolchinol methyl ether to 2,3,4,7-tetramethoxyphenanthrenequinone (3), was synthesized by the route shown in formulas (XXV) ⟶ (XXVIII) (5,12). Repetition of this sequence of reactions starting with the compound (XXIX) ultimately afforded an isomer of the ketone (XXVIII), reduction of

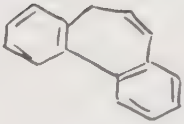


(XVI) (XVII) (XVIII)

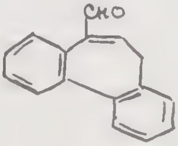
(XX) (XXI) (XIX)



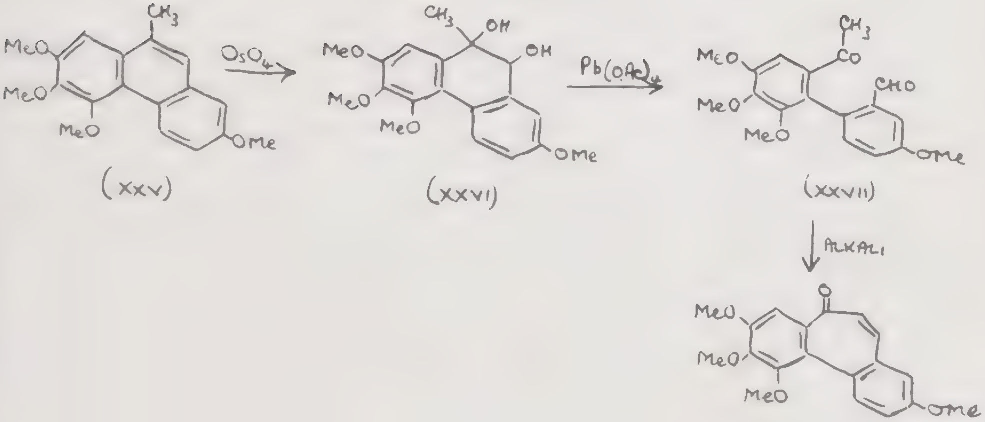
(XXII)



(XXIII)



(XXIV)



(XXV) (XXVI) (XXVII)

(XXVIII)

which gave the saturated ketone (XXX), which was converted through the oxime (XXXI) into the amine (XXXII), and this was resolved into (+) and (–) forms; the *N*-acetyl derivative of the (–) form was shown to be identical with *N*-acetylcolchinol methyl ether (12). (±) Colchinol methyl ether (XXXII) has also been synthesized by another route (18).

Ring-C. Although ring-C in colchinol methyl ether is shown by the above synthesis to be six-membered, there is adequate evidence that it is not so constituted in colchicine itself. It was first suggested by Dewar (13) that this ring in the alkaloid has a seven-membered tropolone-like structure and that colchicine has the constitution (XXXIII) or (XXXIV), and this is supported by the following evidence.

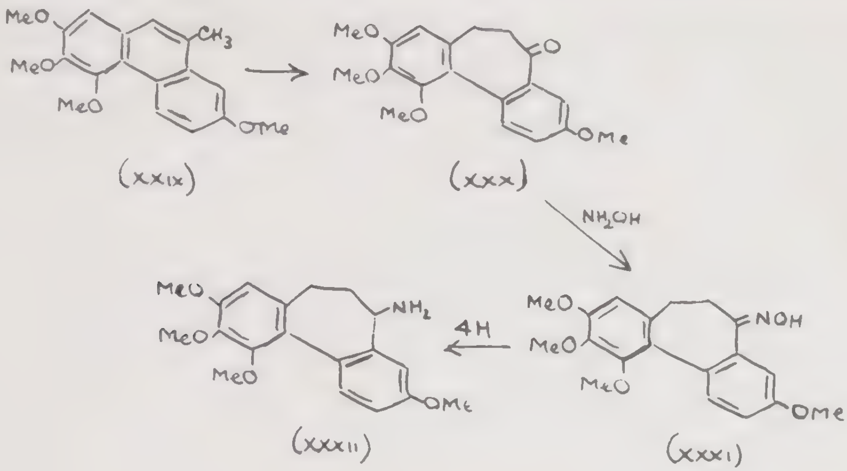
(*a*) Colchicine has ester-like properties, being easily hydrolyzed to colchiceine (XXXVI), which evidently possesses an enolic hydroxyl group.

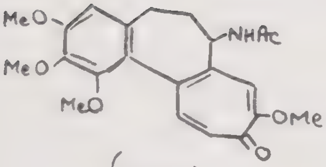
(*b*) Remethylation of colchiceine affords two isomeric methyl ethers, colchicine and isocolchicine, corresponding to the isomeric pair (XXXIII) and (XXXIV).

(*c*) Hydrogenation of colchiceine (XXXVI) affords hexahydrocolchiceine (XXXVII), which still contains an ethylenic double bond since it can be converted into an olefin oxide (2,6). The fully substituted double bond of (XXXVII) would be expected to resist hydrogenation.

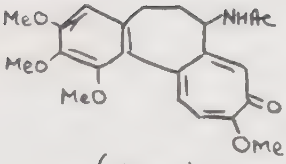
(*d*) Hexahydrocolchiceine (XXXVII) is oxidized like a vicinal diol by lead tetra-acetate (14) and by periodic acid (1); from the products of oxidation by the latter reagent a substance has been obtained that gives a 2,4-dinitrophenylhydrazone (1). This proved to be the derivative of a monoaldehyde, but the cyclization of the initially produced dialdehyde (XXXVIII) to a monoaldehyde such as (XXXIX) would satisfactorily explain this finding.

(*e*) Colchicine possesses no ketonic properties, and in this respect resembles other tropolones and γ-pyrones; however, saturation of two of the double bonds results in the appearance of ketonic activity (as would be expected on the basis of the structure (XXXIII)/(XXXIV)), for tetrahydrocolchicine gives a 2,4-dinitrophenylhydrazone (12).

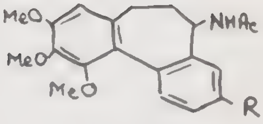




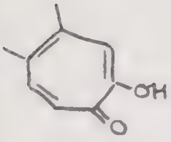
(XXXIII)



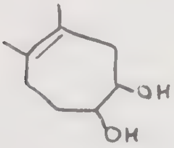
(XXXIV)



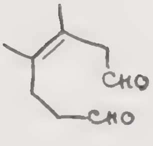
(XXXV)



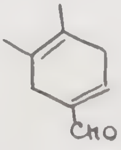
(XXXVI)



(XXXVII)



(XXXVIII)



(XXXIX)

(*f*) Colchicine undergoes benzilic acid rearrangement followed by dehydration on heating with methanolic sodium methoxide, the product being allocolchicine (XXXV, R = COOMe) (19), the structure of which was indicated by conversion in stages (COOMe ⟶ $CONH_2$ ⟶ NH_2 ⟶ OH ⟶ OMe) into *N*-acetylcolchinol methyl ether (XXXV, R = OMe).

(*g*) The previously mentioned conversion of colchiceine on treatment with cold alkaline hypoiodite into *N*-acetyliodocolchinol (identified structurally by reduction to *N*-acetylcolchinol (XXXV, R = OH), obtainable directly from colchiceine by the action of alkali and hydrogen peroxide (7)) may also be formulated as a benzilic acid rearrangement, i.e., (XL) ⟶ (XLIII) (8).

Colchicine may thus be represented by the structure (XXXIII) or by (XXXIV).

A detailed account of the chemistry and biological properties of the alkaloid is given by Cook and Loudon (9).

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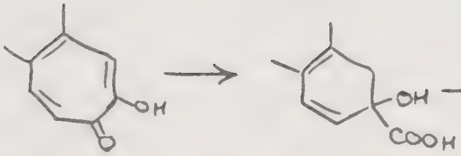
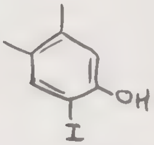


(XL) (XLI) (XLII)



(XLIII)

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CHAPTER 11

BIOGENETIC RELATIONSHIPS

The processes by which alkaloids are synthesized in plants have long been the subjects of study and speculation among organic chemists and biochemists. Little is known about them with certainty, but a study of the molecular structures of the alkaloids and of the substances occurring alongside them in the plants leads to certain firm convictions as to the sort of processes involved.

In a work of this nature presentation is facilitated and greater clarity achieved if the modes of possible biogenesis are set out as connected series of reactions, but it must be clearly understood that this is only done for convenience and that a definite order for the various stages is *not* being assumed. For example, such processes as *O*- and *N*-methylation and acetylation, and *O*:*O*-methylenation may occur at any stage, and the use of an *O*- or *N*-methylated substance during a particular process or series of processes, e.g., the use of methylamine in the synthesis of the alkaloids of the tropane group, simply means that the group *finally* appears in that state, and that methylation may occur at some previous or subsequent stage. Furthermore, the units used in the processes given are specified as formaldehyde, acetone, etc., when what should really be read is "formaldehyde *or its equivalent*" (which could be a carbinolamine —N—CH_2OH, from which H·CHO is virtually available, formic acid + a reducing system, or glycine + an oxidizing system), and "acetone *or its equivalent*" (acetoacetic acid, acetone dicarboxylic acid, citric acid + an oxidizing system, etc.). The determination of the order and details of the biogenetic processes is the task of the biochemist. Robinson (20) has frequently emphasized the above

reservations, and it is with these in mind that this chapter should be read.

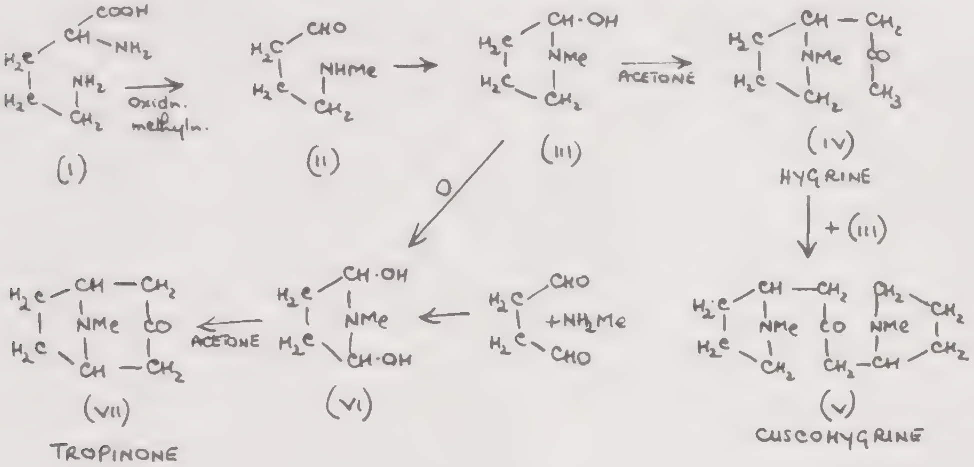
The simple units from which the alkaloids may arise are the amino acids resulting from the decomposition of proteins. Two reactions are regarded as keys to the main process, namely, the aldol condensation of $C{=}O$ with $-CH-C{=}O$ and the similar condensation of carbinolamines, $-C(OH)-N-$ with $-CH-C{=}O$. The amino acid $R-CH(NH_2)-COOH$ can, by decarboxylation, give the amine RCH_2NH_2, and, by oxidation, the aldehyde RCHO, and in this connection it is significant that 1,4-tetramethyldiaminobutane, $Me_2N(CH_2)_4NMe_2$, which is a methylated and decarboxylated ornithine, $H_2N(CH_2)_3CH(NH_2)COOH$, occurs in *Hyoscyamus muticus* and *Hyoscyamus reticulatus* (28).

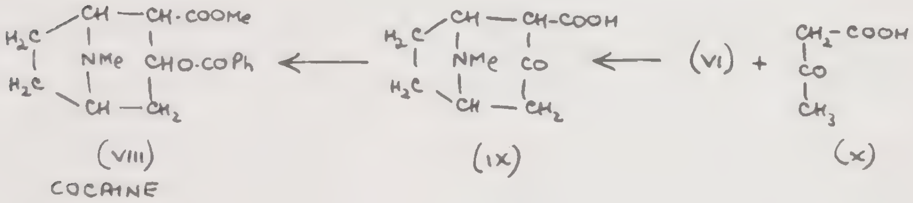
1. ALKALOIDS OF THE PYRROLIDINE GROUP

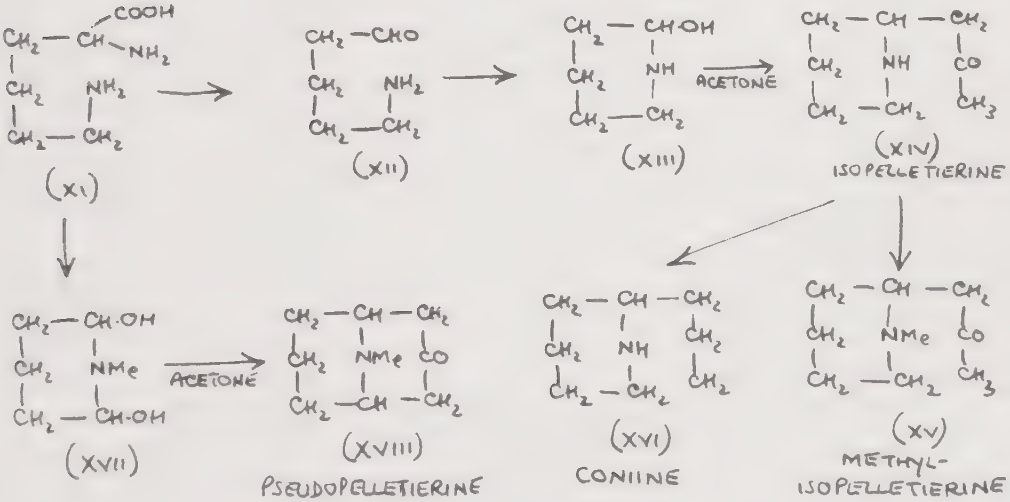
These alkaloids are regarded as being derived from ornithine (I). Hygrine and cuscohygrine could arise as shown in formulas (I) ⟶ (V). Tropinone could arise in a similar way from the base (VI), which could be derived from (III) or could be formed from succindialdehyde, or its equivalent + methylamine. The laboratory analogy for this is the Robinson tropinone synthesis (see Chapter 1), which gives a high yield of tropinone directly (16). The structure of cocaine (VIII) clearly indicates the participation of a carboxylated acetone in the tropinone synthesis, and acetoacetic acid is much the most likely intermediate, (X) ⟶ (IX) ⟶ (VIII). It has been shown that when ornithine-2-C^{14} is fed to *Datura stramonium* radioactive hyoscyamine is formed (13).

2. ALKALOIDS OF THE PIPERIDINE-PYRIDINE GROUP

Strong confirmation of the above views on the origin of the alkaloids of the pyrrolidine group is provided by the occurrence in Nature of a series of ring-homologous bases, presumably derived from lysine (XI). Thus the biogenesis of methylisopelletierine, the ring homolog of hygrine, can be represented by the sequence (XI) ⟶ (XV), and of coniine by (XI) ⟶ (XVI). Similarly, pseudopelletierine may arise by the route (XI) ⟶ (XVII) ⟶ (XVIII), in a manner analogous


Oxidn.
methyln.
(I)
(II)
(III)
ACETONE
(IV)
HYGRINE
+ (III)
O
(VI)
ACETONE
(VII)
TROPINONE
+NH₂Me
(V)
CUSCOHYGRINE


(VIII)
COCAINE
(IX)
(VI) +
(X)


(XI)
(XII)
(XIII)
ACETONE
(XIV)
ISOPELLETIERINE
(XVII)
ACETONE
(XVIII)
PSEUDOPELLETIERINE
(XVI)
CONIINE
(XV)
METHYL-
ISOPELLETIERINE

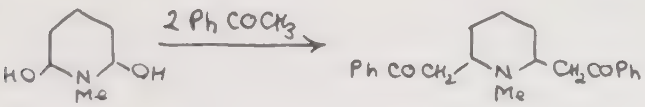
to the origin of tropinone; it has been synthesized in the laboratory from glutaric dialdehyde by a method analogous to Robinson's tropinone synthesis (15).

The Lobelia Alkaloids.

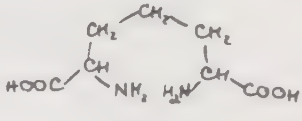
The lobelia alkaloids may arise in a similar way, with acetophenone and methyl ethyl ketone replacing the acetone in the synthesis of pseudopelletierine, and lobelanine (XX) could easily be formed from (XIX) as shown. For this process, as well as for the synthesis of pseudopelletierine, the amino acid involved must be active at both ends and may be a lysine precursor such as diaminopimelic acid (XXI), oxidation of which would furnish glutaric dialdehyde for the production of (XIX). Lysine is formed from aspartic acid via ketodiaminopimelic acid (XXII); reduction of this intermediate followed by dehydration could give (XXIII), and it is interesting that the alkaloid lobinine (XXIV) (the production of which clearly involves one unit of acetophenone and one unit of methyl ethyl ketone) has a corresponding double bond.

The Lupin Alkaloids.

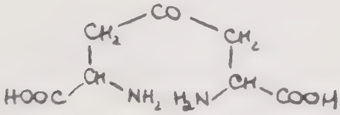
These may be built up from lysine as shown in formulas (XXXV) → (XXX) for lupinine, and (XXXI) → (XXXV) for sparteine (20).



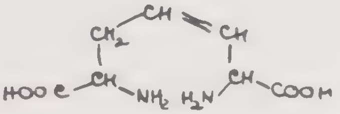
(XIX) ≡ (XVII) (XX)



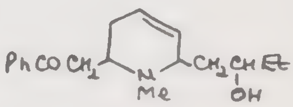
(XXI)



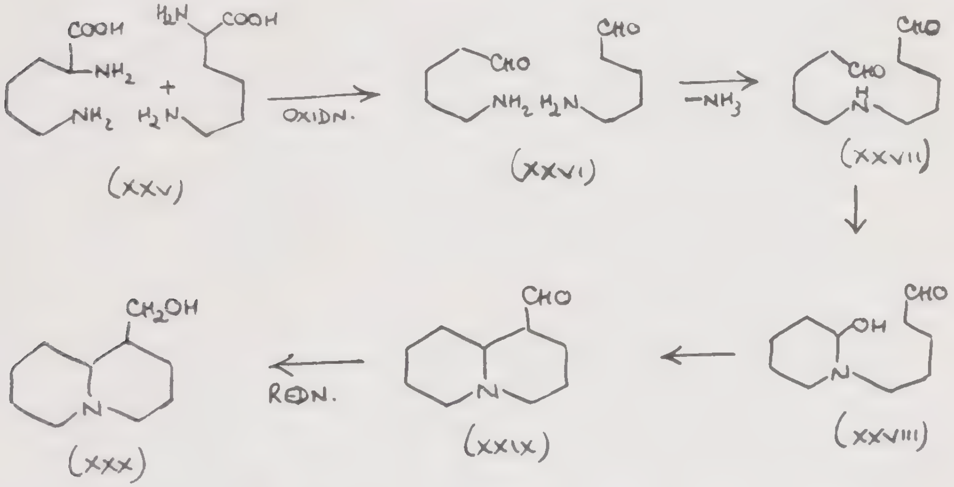
(XXII)

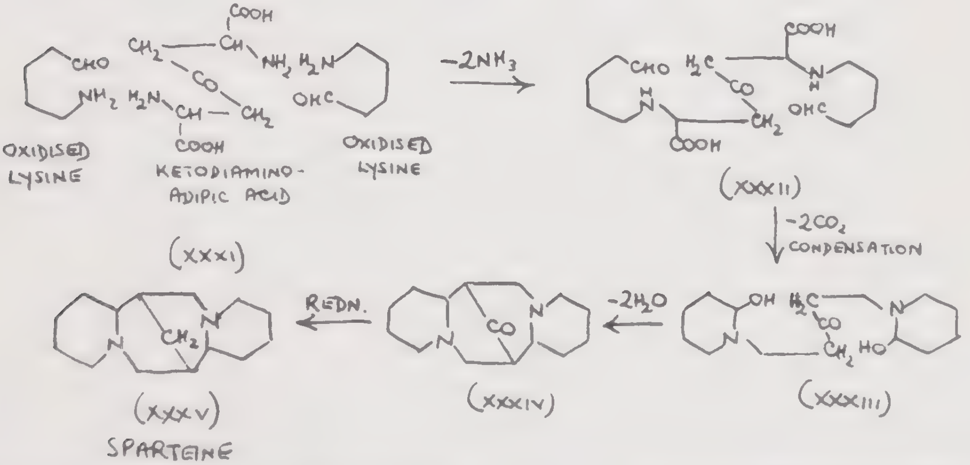


(XXIII)



(XXIV)





Nicotine and Anabasine.

Biochemical feeding experiments have shown that proline and pyrrolidone carboxylic acid can function as the precursor of the pyrrolidine unit of nicotine (8). The β-substitution of the pyridine ring may be explained by assuming activation by a γ-keto group, or by a 1,2-double bond, in a piperidine-type precursor; e.g., nicotine could arise as shown in formulas (XXXVI) ⟶ (XL) (20).

Schöpf (26) has shown that the base (XXXVIII) condenses with itself yielding tetrahydroanabasine (XLI).

3. ALKALOIDS OF THE ISOQUINOLINE GROUP

A. The Benzylisoquinolines.

The alkaloids of this group are, in the main, regarded as being derived from dihydroxyphenylalanine; the general type of synthesis may be illustrated by the formation of laudanosine and papaverine through the intermediates (XLII), (XLIII), (XLIV), and (XLV) (29).

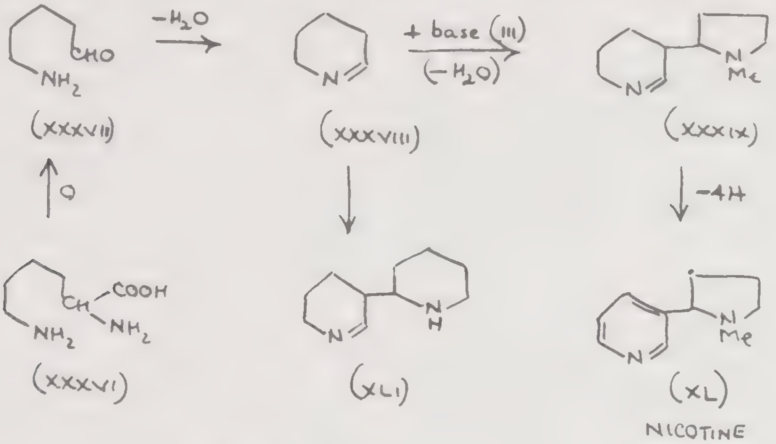
From the norlaudanosine type of system so formed the other groups of isoquinoline alkaloids may be elaborated by reasonable processes.

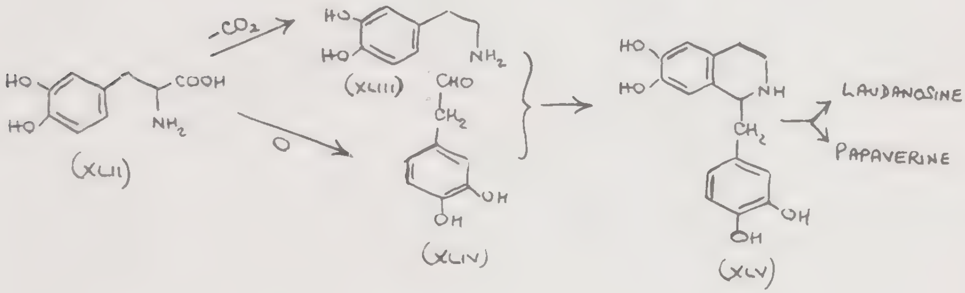
B. The Aporphines.

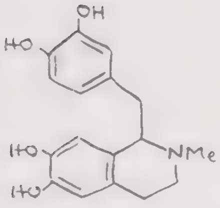
The alkaloids of the aporphine group may be obtained by the removal of hydrogen as shown in (XLVI) ⟶ (XLVII); this type of oxidation has not yet been achieved in the laboratory, only products of the pyrrocoline type such as (XLVIII) being obtained (23,25) (see Chapter 3); it is interesting to note that alkaloids of this type have recently been found in Nature (10).

C. The Tetrahydroberberines.

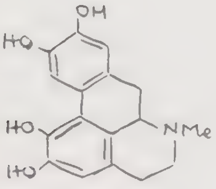
These alkaloids are accessible by the introduction, probably through formaldehyde, of a bridge carbon atom. In Nature this usually takes place *ortho* to hydroxyl, but in the laboratory the reaction



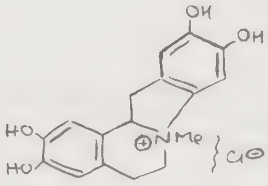




(XLVI)



(XLVII)



(XLVIII)

goes *para* to hydroxyl, e.g., the production of canadine and berberine, (XLIX) ⟶ (LII) (see also Chapter 3).

D. The Phthalideisoquinolines.

Methylation of the nitrogen atom of canadine (LI) followed by oxidation could readily give rise to hydrastine (LIII), and it is noteworthy that hydrastine and berberine occur together in *Hydrastis canadensis*.

E. The Protopine Alkaloids.

Less vigorous oxidation of the tetrahydroberberine system than is required to give phthalideisoquinolines could lead to alkaloids of the protopine group, e.g., the formation of ophiocarpine (LIV) from canadine could be followed by hydration at the reactive 1,2-position of the isoquinoline nucleus to bases of the type (LV), dehydration of which would give such alkaloids as cryptopine (LVI) (14).

F. The α-Naphthaphenanthridines.

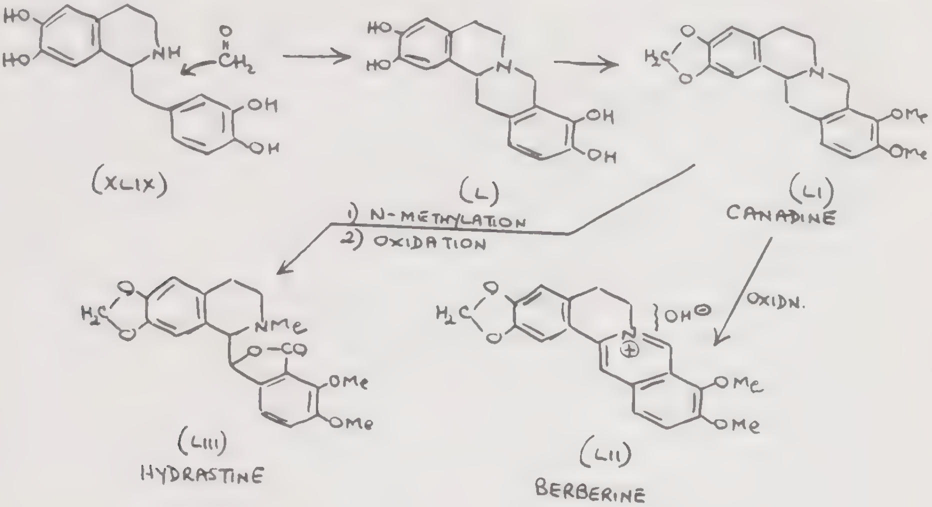
Robinson (20) suggests that these alkaloids may arise as berberine modifications, with scission at the dotted line in (LVII) followed by cyclization between the two asterisked carbon atoms. Manske (14), however, favors formation of the bases from dihydroxyphenylacetaldehyde, with aldol condensation to (LVIII), cyclization to (LIX), amination and bridging by formaldehyde. This process would account for the formation of a —CH(OH)— group in the final product (asterisk in (LIX)) in the position in which such a group is found in chelidonine.

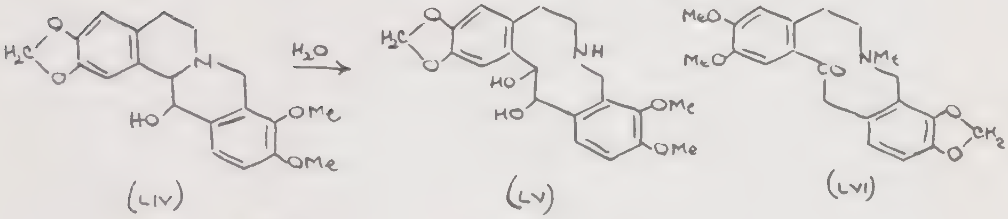
G. Emetine.

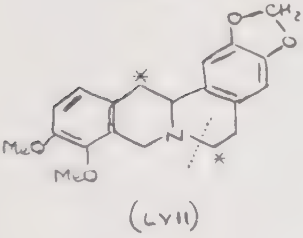
The origin of emetine is discussed with that of strychnine.

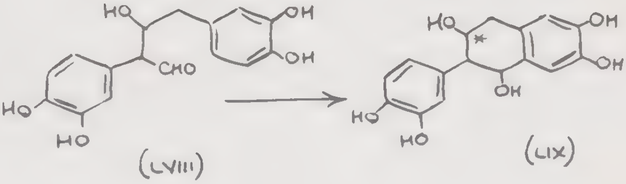
4. ALKALOIDS OF THE MORPHINE GROUP

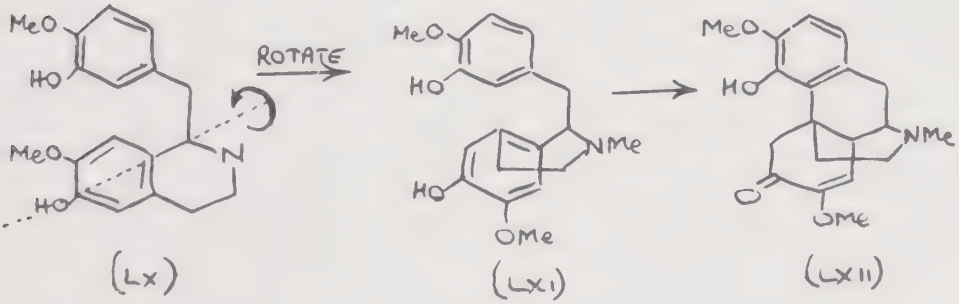
The alkaloids of the morphine group clearly arise from those of the benzylisoquinoline group (4). Robinson suggested that sinomenine (LXII) may be formed from "protosinomenine" (LX) as shown; the base (LX) has been synthesized but in quantities insufficient for further study (22).


HO
HO
NH
O
CH₂
OH
OH
(XLIX)
HO
HO
N
OH
OH
(L)
H₂C
O
O
N
OMe
OMe
(LI)
CANADINE
1) N-METHYLATION
2) OXIDATION
OXIDN.
H₂C
O
O
NMe
O—CO
OMe
OMe
(LIII)
HYDRASTINE
H₂C
O
O
N
⊕
OH⊖
OMe
OMe
(LII)
BERBERINE


H₂C
O
O
N
HO
OMe
OMe
(LIV)
H₂O
H₂C
O
O
NH
HO
HO
OMe
OMe
(LV)
MeO
MeO
NMe
CO
O
O
CH₂
(LVI)

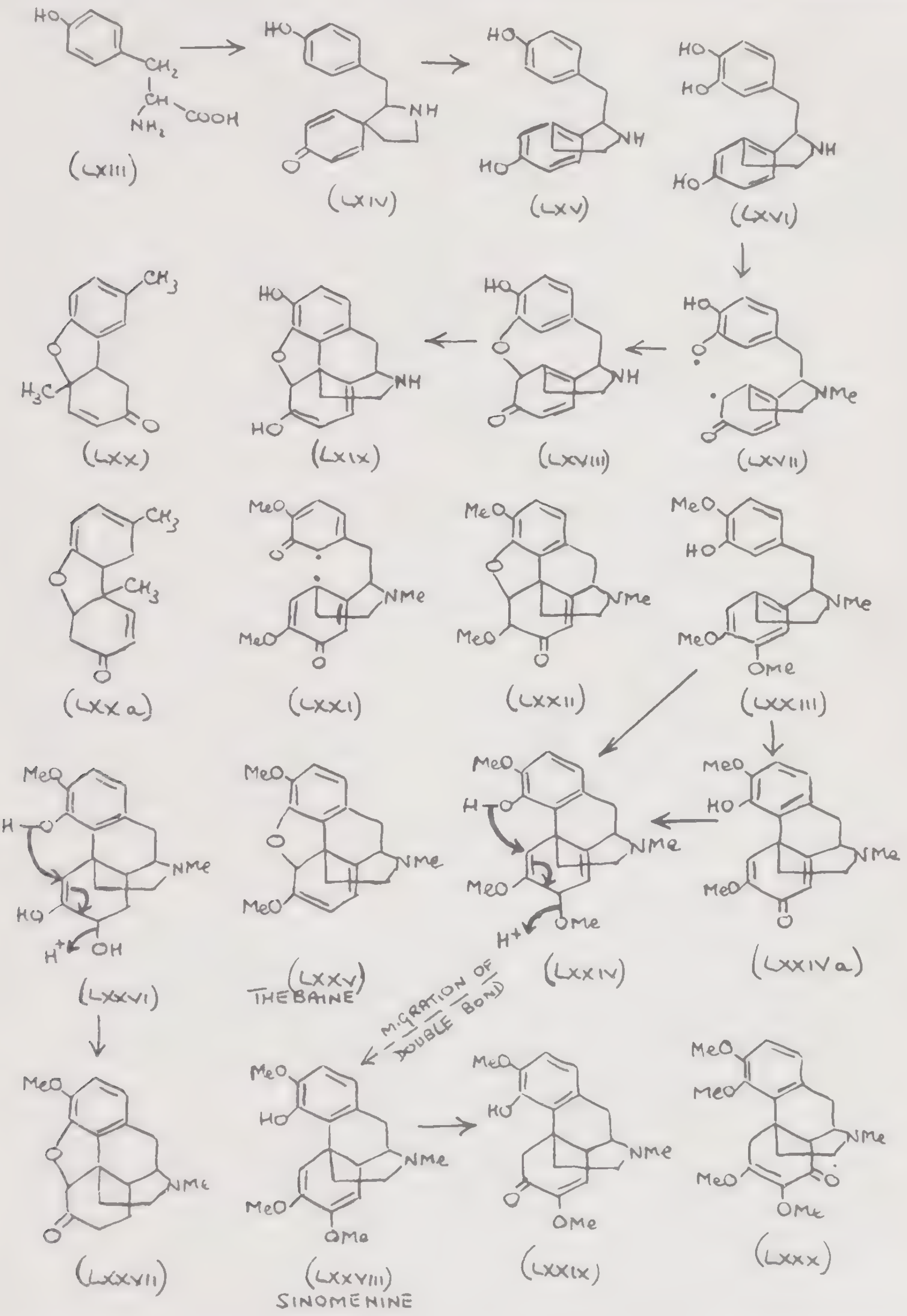

O—CH₂
O
*
*
N
MeO
MeO
(LVII)


HO
OH
OH
CHO
HO
HO
(LVIII)
HO
*
OH
OH
OH
HO
HO
(LIX)


MeO
HO
MeO
HO
N
ROTATE
(LX)
MeO
HO
NMe
HO
OMe
(LXI)
MeO
HO
NMe
O
OMe
(LXII)

On the basis of the supposed oxidation of *p*-cresol to (LXX), Schöpf (24) suggested that the alkaloids containing the typical 4,5-oxide bridge of morphine might arise as shown in (LXVI) ⟶ (LXIX) from trioxyisoquinolines (which themselves could arise as shown in (LXIII) ⟶ (LXVI) (17,20)). However, the oxidation of *p*-cresol has been shown to give the ketone (LXXa) and if the morphine alkaloids are produced by an analogous process, radical pairing in (LXXI) must be involved giving the intermediate (LXXII) (3), from which the other bases of the morphine group may be derived.

However a radical substitution reaction might occur with laudanine (LXXIII) to give the intermediate (LXXIV) directly, or through (LXXIVa), and this could suffer closure of the 4,5-oxide bridge by allylic expulsion of a methoxyl group (5,6). There is an analogy for this process in the formation of (+)-dihydrocodeinone (LXXVII) on heating dihydrosinomeninone (LXXVI) with acids. Thebaine would be the product of the processes set out in (LXXIII) ⟶ (LXXIV) ⟶ (LXXV), but the migration of the 8,14-double bond in (LXXIV) would give (LXXVIII), in which such an allylic expulsion of methoxyl could not occur, and (LXXVIII) would give sinomenine (LXXIX) on hydrolysis. Thus thebaine (and from it the other alkaloids of the morphine-thebaine group) and sinomenine could arise in a simple manner from the two enantiomorphic forms of laudanine. This sequence of processes affords a simple explanation of why the only alkaloids of the morphine group that do not contain the 4,5-oxide bridge (sinomenine (LXXIX) and hasubanonine (LXXX)) are substituted at position 7, whereas no bases containing this bridge have been found with substituents in this position (5).


(LXIII)
(LXIV)
(LXV)
(LXVI)
(LXX)
(LXIX)
(LXVIII)
(LXVII)
(LXX a)
(LXXI)
(LXXII)
(LXXIII)
(LXXVI)
(LXXV)
THEBAINE
(LXXIV)
(LXXIVa)
MIGRATION OF DOUBLE BOND
(LXXVII)
(LXXVIII)
SINOMENINE
(LXXIX)
(LXXX)

5. THE ERYTHRINA ALKALOIDS

The erythrina alkaloids contain a morphine-like blocked hydroaromatic system and could arise from dihydroxyphenylalanine via the base (LXXXI) and the subsequent stages shown in (LXXXI) ⟶ (LXXXVII) (7,12,20). β-Erythroidine and the α-isomer are doubtless formed as the result of fission of the catechol nucleus of (LXXXVII) by some process similar to that proposed as one of the stages in the biogenesis of strychnine and emetine.

6. ALKALOIDS OF THE INDOLE AND QUINOLINE GROUPS

The alkaloids of this group are, in general, believed to be derived from tryptophan (LXXXVIII).

A. The Harmala Alkaloids.

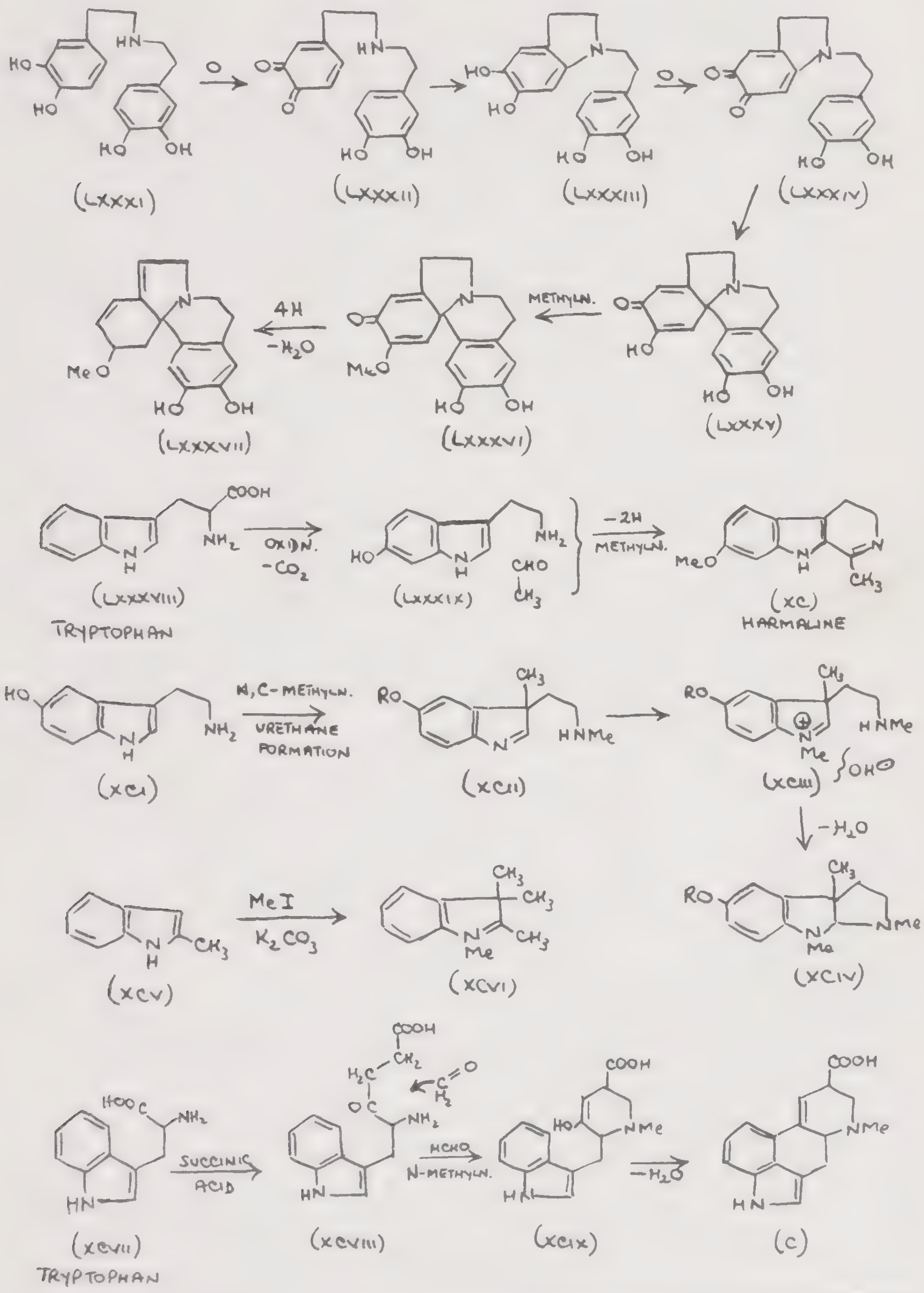
These are presumably derived by a ring closure process analogous to that involved in the formation of isoquinoline alkaloids, e.g., the synthesis of harmaline (XC) from tryptophan (LXXXVIII); oxidation of harmaline would then give harmine.

B. Physostigmine.

This alkaloid presumably is derived from tryptophan via 5-hydroxytryptamine (XCI) as shown in (XCI) ⟶ (XCIV), where R = MeNH·CO—. Laboratory analogies for the methylation of the indole β-carbon atom are known, e.g., the methylation of (XCV) to (XCVI) (see Elderfield (9)).

C. The Ergot Alkaloids.

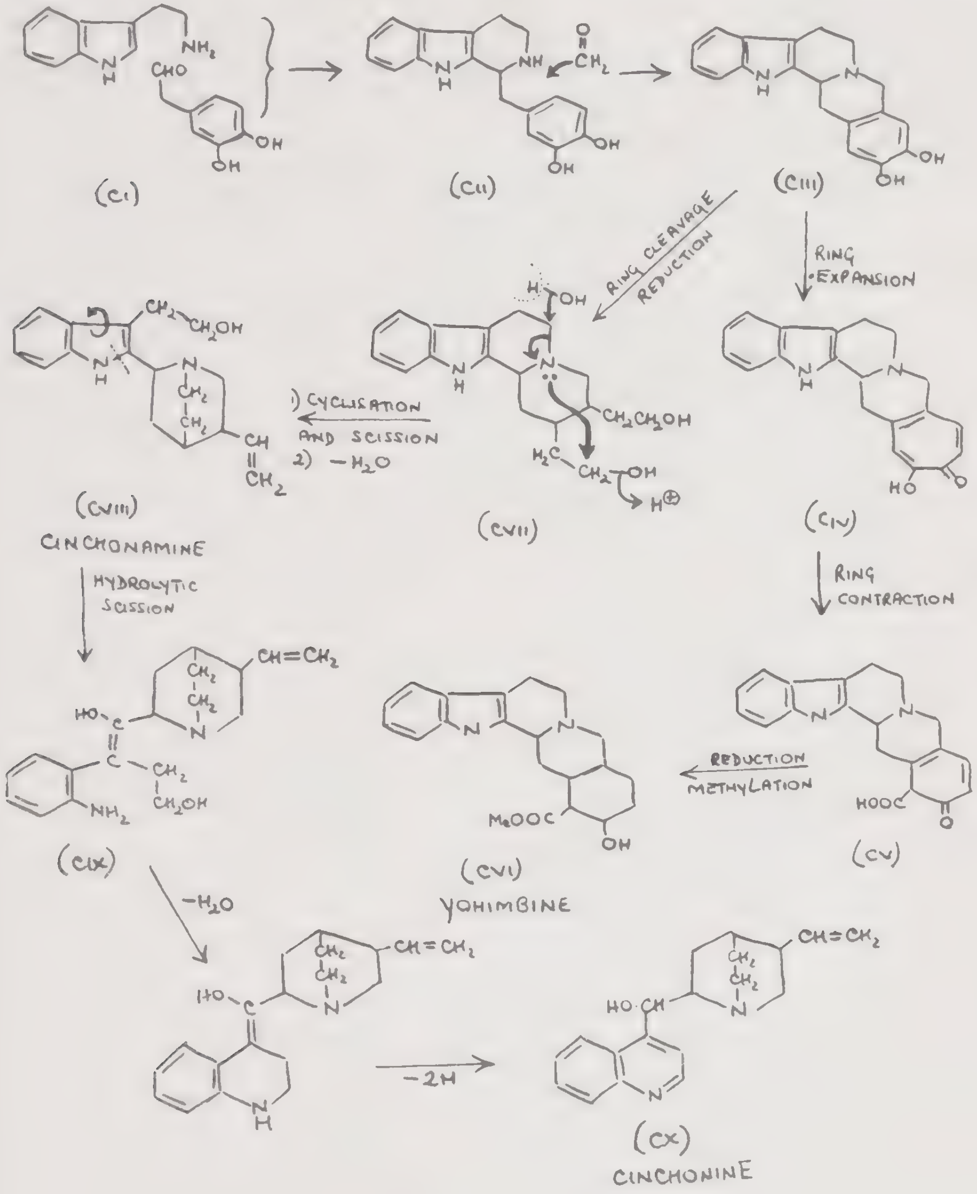
The ergot alkaloids are all derivatives of lysergic acid, or of the diastereoisomeric isolysergic acid, and these acids may well arise from tryptophan as shown in formulas (XCVII) ⟶ (C) (20). An analogy for the first step of this sequence is the formation of aminolaevulinic acid from succinic acid and glycine.


(LXXXI)
(LXXXII)
(LXXXIII)
(LXXXIV)
(LXXXV)
METHYLN.
(LXXXVI)
4H
$-H_2O$
(LXXXVII)
(LXXXVIII)
TRYPTOPHAN
OXIDN.
$-CO_2$
(LXXXIX)
CHO
CH_3
$-2H$
METHYLN.
(XC)
HARMALINE
(XCI)
N,C-METHYLN.
URETHANE FORMATION
(XCII)
(XCIII)
$OH^{\ominus}$
$-H_2O$
(XCIV)
(XCV)
MeI
K_2CO_3
(XCVI)
(XCVII)
TRYPTOPHAN
SUCCINIC ACID
(XCVIII)
HCHO
N-METHYLN.
(XCIX)
$-H_2O$
(C)

D. Yohimbine and Cinchonine.

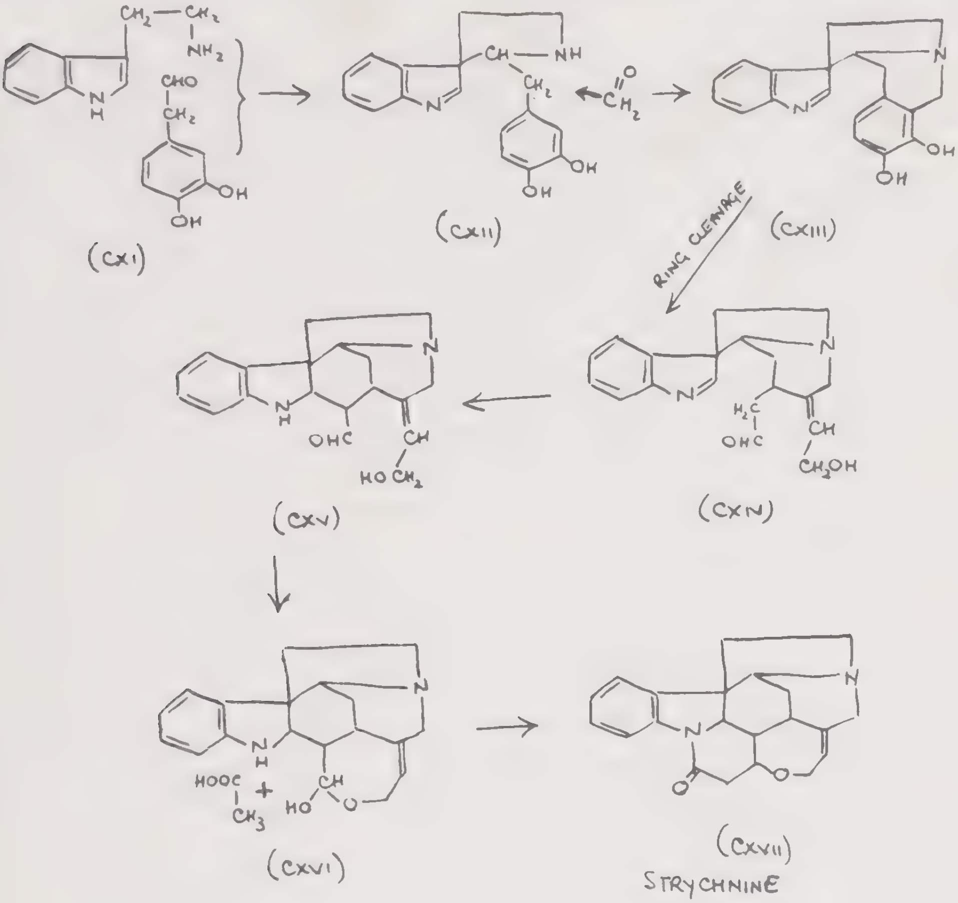
The skeleton of yohimbine can be built up from tryptamine and dihydroxyphenylalanine, with the introduction of a berberine-bridge carbon atom, processes exactly analogous to the formation of canadine, i.e., (CI) → (CIII) (2). The —COOMe group, which is a marked feature of the alkaloids of the yohimbine type, is believed to arise by the introduction of an extra carbon atom into the catechol ring giving a tropolone (CIV) which crumples to a keto acid (CV); reduction and methylation of the —COOH group then gives yohimbine (CVI) (19,20).

The reaction intermediate (CIII) may be further modified so as to give a logical sequence of processes leading successively to bases of the cinchonamine and cinchonine groups (11,27). Cleavage of the catechol nucleus of (CIII) followed by reduction could lead to the base (CVII); subsequent cyclization of one of the —CH_2CH_2OH groups with the nitrogen atom would result in the formation of the quinuclidine system and opening of the piperidine ring with the appearance of CH_2CH_2OH at the β-position of the indole system; simultaneous dehydration would account for the presence of the vinyl group in the cinchona alkaloids. The product of this sequence of reactions would then be cinchonamine (CVIII), which could be further converted into cinchonine (CX).


(CI)
(CII)
(CIII)
RING CLEAVAGE REDUCTION
RING EXPANSION
(CVIII)
CINCHONAMINE
1) CYCLISATION AND SCISSION
2) −H₂O
(CVII)
(CIV)
RING CONTRACTION
HYDROLYTIC SCISSION
REDUCTION
METHYLATION
(CIX)
(CVI)
YOHIMBINE
(CV)
−H₂O
−2H
(CX)
CINCHONINE

E. Strychnine.

The fission of a catechol nucleus as postulated in the biogenesis of the cinchona alkaloids was first postulated by Woodward (30) in connection with the biogenesis of strychnine. If the reaction between tryptamine (CXI) and 3,4-dihydroxyphenylacetaldehyde takes place with attack of the indole nucleus at the β-position the product will be (CXII). Introduction of a berberine-bridge carbon atom then leads to (CXIII). At this stage fission of the aromatic nucleus between the two hydroxyl groups is assumed and other slight modifications occur leading to (CXIV). The subsequent stages present no difficulties; cyclization of (CXIV) to the Wieland-Gumlich aldehyde (CXV) is a normal process for which there are many analogies, and this aldehyde, possibly in the semi-acetal form (CXVI), condenses with acetic acid to give strychnine (CXVII). The last of these stages has been accomplished in the laboratory (1,21).


(CXI)
(CXII)
(CXIII)
RING CLEAVAGE
(CXIV)
(CXV)
(CXVI)
(CXVII)
STRYCHNINE

F. Emetine.

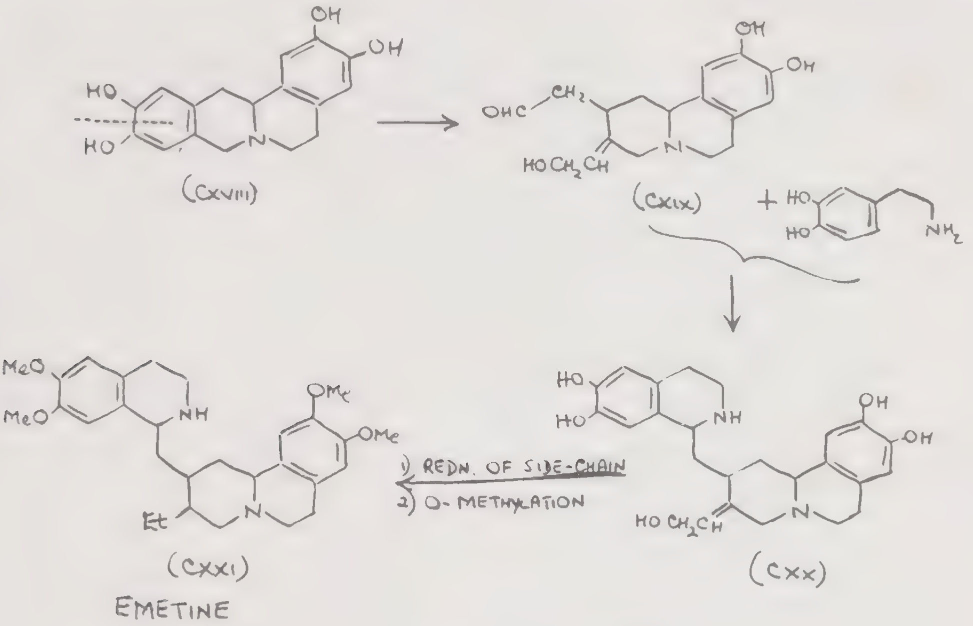
A very striking outcome of the above revolutionary postulate of the fission of an aromatic nucleus during the biogenesis of strychnine was the development, on biogenetic grounds, of a structure for emetine that has been proved by degradation to be correct. The starting point of the biogenesis of this alkaloid is presumably the tetrahydroberberine alkaloid (CXVIII), which could suffer opening of the aromatic nucleus in a manner analogous to the transformation of (CXIII) to (CXIV), giving the aldehyde (CXIX). The condensation of the aldehyde with dihydroxyphenylethylamine, as in the laudanosine synthesis, would then give the base (CXX), from which emetine could arise by methylation of the hydroxyl groups and reduction of the side chain (18,20).

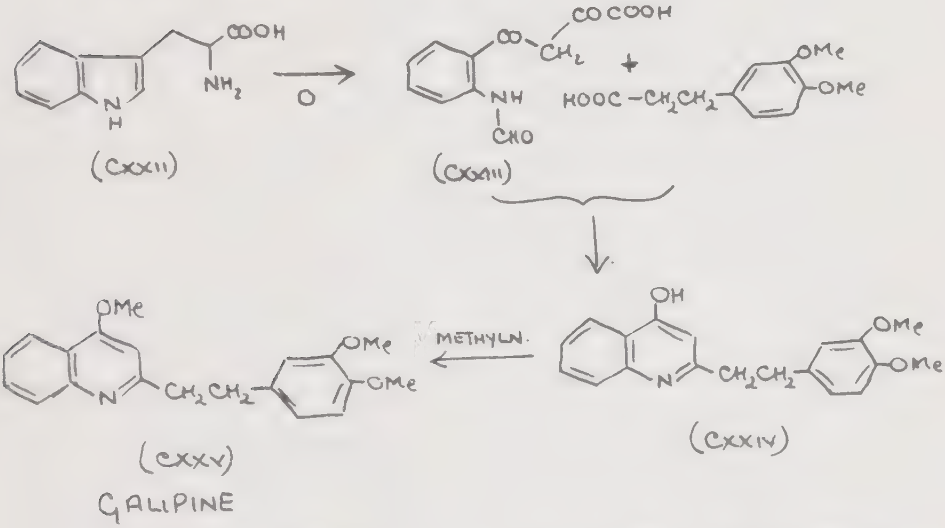
G. Other Alkaloids.

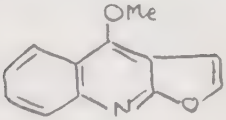
Of the other alkaloids discussed in the preceding chapters bases of the galipine type presumably arise from tryptophan through the known oxidation product (CXXIII); e.g., the synthesis of galipine by the route (CXXII) → (CXXV) seems likely (20).

Furanoquinolines such as dictamnine (CXXVI) are also presumably derived from tryptophan, but the origin of the furan ring remains obscure, though it may be formed from the CO·COOH part of the keto-acid (CXXIII) (20).

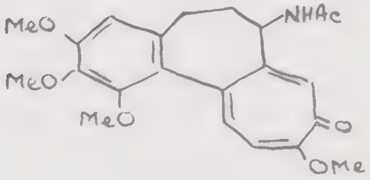
The origin of colchicine (CXXVII) remains obscure; no relationship with any other group of alkaloids can be detected.







(CXXVI)



(CXXVII)

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